IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner: Michele C. Flood
Christopher O. Okunji, et al.	Group Art Unit: 1655
Serial No.: 09/428,203	
Filing Date: October 27, 1999	
For: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS OF EXTRACTING THE COMPOUNDS	

APPEAL BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants submit the following Appeal Brief. This brief is timely filed within the 5th extension period that expires on March 14, 2011. A petition for a 5 month extension of time accompanies this Brief. Please note that Applicants had previously filed a Notice of Appeal on November 28, 2008, followed by an Appeal Brief on May 22, 2009. The Examiner reopened prosecution on November 16, 2009 and issued a Final Rejection on June 4, 2010. This Appeal Brief is being filed pursuant to the Notice of Appeal filed on August 14, 2010 and in response to the Examiner's Final Rejection. Applicants hereby respectfully request that the previously paid Appeal Brief fee be applied to the filing of the present Appeal Brief. The Commissioner is hereby authorized to charge any fees that are required, as well as any additional fees that may be required in connection with the filing of this paper, or credit any overpayment, to U.S. Army Medical

Research and Materiel Command, Deposit Account Number 210380. Please send all correspondences to Ms. Elizabeth Arwine, Esq.; Office of the Staff Judge Advocate; U.S. Army Medical Research and Materiel Command; 504 Scott Street; Fort Detrick, MD 21702-5012, Attn: MCMR-JA (Ms. Arwine). Please direct any questions regarding this case to Ms. Abanti (Abby) Bhattacharyya, Esq., at (410) 964-9553.

Sincerely,

March 14, 2011
Date

Abanti A Bhattacharyya, Esq.
Reg. No. 36,681

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APPEAL BRIEF

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I. REAL PARTY IN INTEREST

The real party in interest is U.S. Army Medical Research and Materiel Command of Fort Detrick, Maryland.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences that will affect or be affected by the outcome of this appeal.

III. STATUS OF THE CLAIMS

For the purposes of this Appeal, Applicants provide a status of the claims that conforms with the amendment of March 16, 2010. Thus, the present application recites claims 1 through 40. Claim 1 is currently pending in this application. Claims 2 through 10 are cancelled. Claim 11 is currently pending in this application. Claims 12 through 29 are cancelled. Claim 30 is currently pending in this application. Claims 31 through 37 are cancelled. Claim 38 is currently pending in this application. Claims 39 through 40 are cancelled. For the purposes of this Appeal, Applicants respectfully request that only the claims of the entered amendment of March 16, 2010, claims 1, 11, 30 and 38, be considered.

IV. STATUS OF THE AMENDMENTS

An amendment and response was filed by Applicants on July 24, 2008, in response to the Examiner's final rejection of March 28, 2008. The amendment and response was not entered. Thereafter, Applicants filed a Notice of Appeal on November 28, 2008, and subsequently an Appeal Brief on May 22, 2009. Thereafter, on November

16, 2009, the Examiner reopened prosecution , entering the amendment of July 24, 2008 and issuing a non-filing rejection. Applicants filed a response to the non-final rejection under 37 CFR §1.111 on March 16, 2010. The Examiner issued a final rejection of claims 1, 11, 30 and 38 on June 4, 2010. Applicants filed a second Notice of Appeal on August 14, 2010. For the purposes of this Appeal, Applicants respectfully request that only the claims of the now entered amendments of July 24, 2008 and March 16, 2010 claims 1, 11, 30 and 38, be considered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is directed to a saponin-enriched fractionated extract of *Napoleonaea imperialis* that exhibits aniti-leishmanial activity. The extract has been effective in treating *Leishmania* while having low-toxicity for humans. *See* Specification at 14. The recitation in claim 1 is based upon findings that traditional medicines may provide efficacy against protozoan infections without the side-effects encountered when utilizing conventional pharmaceuticals. Claim 11 is dependent upon claim 1 and recites direct solvent extraction of the powdered seeds of *Napoleonaea imperialis*. Direct solvent extraction of the powdered seeds was found to be the most effective technique to extract the saponin-enriched fraction recited in claim 1. *See id.* The extraction was conducted in three batches utilizing the solvents hexane, chloroform, ethyl acetate and methanol. The methanol extract was found to be the most active fraction and is recited in claim 30, which is dependant upon claim 1, and claim 38, which is dependant upon claim 11.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed in this appeal are as follows:

(A) Are claims 1, 11, 30 and 38 unpatentable as being anticipated by Kapundu et al. because Kapundu et al."inherently" discloses each limitation of the claimed invention by functioning in accordance with, or include the claim limitations even though Kapundu does not expressly teach "a biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, exhibiting anti-leishmanial activity?

(B) Has the Examiner erred in applying the "inherency" doctrine in a final rejection of Applicants' claims 1, 11, 30 and 38 as being anticipated by Kapundu et al?

(C) Is the term "fractionated," as recited in claim 1, sufficiently outside of the scope of the term "fractionating" to support the Examiner's position that it provides sufficient grounds for requiring an additional search leading to the final rejection of claims 1, 11, 30 and 38 in the Examiner's Action of June 4, 2010?

(D) Is the Examiner's reopening of prosecution to enter an amendment and finally reject the claims after submission of an Appeal Brief proper under MPEP §1207.04 when:

(i) The action is used to reapply a reference raised by the Examiner in previous office actions and omitted in subsequent Office actions; and

(ii) Does the omission of the reference in subsequent Office actions and a telephonic interview indicating allowability "absent the discovery of prior art that reads

on the claimed invention" act as an implied waiver of the requirement under MPEP § 707.07(e) (Noting All Outstanding Requirements) and MPEP §704.10 (Waiver of the Requirement)?

VII. ARGUMENT

Errors of Law and Fact

We begin by presenting the relevant portions of the prosecution history of this application to date:

The Kapundu et al reference was first raised by the Examiner in her Office Action of October 25, 2002 to the parent application. It was then raised in the RCE non-final Office Action of May 30, 2007. However, in the Office Action of March 28, 2008, the prior art rejection of the claims are based on another reference and Kapundu et al is not mentioned. In subsequent communications with the Examiner, namely a telephonic interview, Examiner explicitly notes (in the Interview Summary Record of July 24, 2008) that agreement was reached with respect to the claims: "Applicant's representative, Abby Bhattacharyya, proposes limiting the species recited in Claim 1 to *Napoleonaea imperialis* and cancelling Claims 2-10, 12-29 and 31-35. Amending the claims as discussed would appear to obviate *the rejections of record* (emphasis added) and place Claims 1, 11, 30 and 38 in condition for allowance absent discovery of prior art that reads on the claimed subject matter." *See* Interview Summary Record of July 24, 2008, Substance of Interview.

The Examiner notes that the only condition against allowance would be the discovery of prior art that reads on the claimed invention. It is particularly important to

note that inherent in the Examiner's statement is the distinction of the prior art already of record (already overcome) and the discovery of prior art (implying applying new art). However, the Examiner issued an Advisory Action on August 21, 2008 stating that the amendment was not entered because "Applicant's insertion of the limitation "fractionated" would require further search and/or consideration". *See* Advisory Action at Note 3 (August 21, 2008 and October 10, 2008). Applicants filed an Appeal Brief on May 22, 2009 on several grounds including the fact that the term "fractionated" was suggested by the Examiner in the Office Action of March 28, 2008 which then initiated the telephonic interview and the Applicants' reliance on the Examiner's explicit statements made in the Interview Summary Record. Kapundu et al is not mentioned in any of these communications. On November 16, 2009, the Examiner reopened prosecution on its merits, entering the claims 1, 11, 30 and 38 and rejecting them on Kapundu et al. in a newly applied non-final rejection. Applicants replied under 37 CFR §1.111 rebutting the Examiner's arguments on Kapundu et al on the grounds that the Examiner had indicated allowability previously and on the grounds that the Examiner had not substantiated her new inherency rejection based on Kapundu et al. The Examiner issued a final rejection of claims 1, 11, 30 and 38 (claim 38 is not explicitly stated in the art rejection) on June 4, 2010 where the Examiner notes, "However, with regard to the Interview Summary" mailed dated July 24, 2008, the record does not indicate the term "fractionated" was discussed, let alone any mention of the Examiner suggesting Applicant to amend the claims to recite "fractionated." See Examiner's Office Action of June 4, 2010, page 6. Applicants filed a Notice of Appeal on August 14, 2010. The present Appeal Brief results therefrom.

(A) Are claims 1, 11, 30 and 38 unpatentable as being anticipated by Kapundu et al. because Kapundu et al."inherently" discloses each limitation of the claimed invention by functioning in accordance with, or include the claim limitations even though Kapundu does not expressly teach "a biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, exhibiting anti-leishmanial activity?

The metes and bounds of inherency in establishing patentability as been discussed in case law. Although not precedent setting, in *Sanofi-Aventis v. Sandoz*, the Court held that the Examiner had been correct in allowing the case, as inherency had not been established when the prior art taught a 90% pure oxaliplatin and applicants claimed an "optically pure" composition. See *Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, 345 Fed. Appx. 594 (2009).

The course of prosecution of the present application appears to show that it is the Examiner's contention that, as in *Gleave*, "discovery of a new property or use of a previously known composition cannot impart patentability to a composition." See *In re Gleave* 560 F. 3d 1331 (2009) citing *In re Sprada* 911 F 2d. 705, 708 (Fed. Cir. 1990). The Examiner likely believes that her inherency argument is supported by Kapundu et al's teaching of an intermediate methanolic extraction step. However, the present Applicants are not claiming a new property or use of a previously known composition. Rather, the present Applicants recite a direct methanolic extraction of the powdered seeds of *N. imperialis* as it is shown to provide a unique composition that is effective in the treatment of a debilitating disease, leishmania, similar to the purity standard established by *Sanofi-Aventis*. See also *In re Schoenwald* 964 F. 2d, 1122, 1124 (Fed. Cir. 1992).

Applicants' omission of a hydrolysis step, an required step of Kapundu et al. provides a composition having strong antileishmanial properties, as repeatedly argued by Applicants and discussed in the Applicant's §1.132 Affidavit. See Christopher O. Okunji, Rule 1.132 Declaration (June 4, 2004). If one were to find inherency in the existence of a common step, then one embarks upon the road of "thousands of theoretically possible compounds" an argument "contrary to the purpose sought to be effectuated by patent law." See *In re Gleave, Reply Br. 7-8, citing In re Wiggins*, 488 F.2d 538, 543 (CCPA 1973). Thus, the Examiner's position that Kapundu et al inherently anticipates Applicants' present invention is not supported by case law.

Alternatively, an "express teaching" in the absence of a factual basis or a basis in fact and/or technical reasoning to reasonably support that the allegedly inherent characteristic flows from the teachings of the prior art does not establish inherency. See Examiner's Action at 5 (June 4, 2010). This is the core concept of *In re Wiggins* line of cases cited above. An "express teaching," in vacuum, creates "a list of thousand of theoretically possible compounds within the level of ordinary skill in the art" but does not provide a factual basis or a flow from the teachings of the prior art that can sustain a position of inherency. See Id. Such is the case with the Examiner's present argument with respect to the Kapundu et al disclosure of a methanolic precipitation step. Taken exclusively, the step rises to the level of an "express teaching" but the totality of the disclosure of Kapundu et al provides a myriad list of possible compounds. Thus, Kapundu et al cannot provide the necessary technical reasoning to reasonably support the alleged inherent characteristics flows from the teaching of the prior art.

(B) Has the Examiner erred in applying the "inherency" doctrine in a final rejection of Applicants' claims 1, 11, 30 and 38 as being anticipated by Kapundu et al?

The Examiner stated that "the claim-designated plant comprises saponin...the claim-designated functional effect is considered inherent to the extract taught by Kapundu because the source of the plant, the particular plant material from the source plant and the solvent used in the making of the plant extract taught by Kapundu are one and the same as disclosed by Applicant. *See* Examiner's Office Action at 4 (November 16, 2009). Furthermore, the Examiner stated, "While Kapundu does not teach identification of compounds contained therein the methanolic seed extract, thus *necessitating* (emphasis added) a hydrolysis step of the extract, such disclosure by Kapundu does not negate the fact that Kapundu expressly teaches a methanolic extract obtained from powdered seeds of the claim-designated plant containing a saponin fraction therein. Therefore, while Kapundu does not expressly teach that the prior art methanolic plant extract has biological activity *per se*, biological activity is inherent to the extract taughty by Kapundu because the source of the plant, the particular plant material from the source plant, and the solvent used in the making of the plant extract taught by Kapundu are one and the same as instantly claimed by Applicant. Therefore, ...powdered seeds of *Napoleonaea imperialis* taught by Kapundu is inherent to the referenced extract, absent evidence to the contrary." *See* Examiner's Action at 5 (June 4, 2010).

In order to invoke the standard of inherency there must be a basis in fact and/or technical reasoning to reasonably support that the allegedly inherent characteristic flows from the teachings of the prior art. *See* MPEP §2112 and §2112.01. Applicants have

consistently maintained that the Examiner has failed to meet her burden under this standard.

The Examiner's position that "the claim-designated plant comprises saponin...the claim-designated functional effect is considered inherent to the extract taught by Kapundu because the source of the plant, the particular plant material from the source plant and the solvent used in the making of the plant extract taught by Kapundu are one and the same as disclosed by Applicant. *See* Examiner's Action at 5 (June 4, 2010).

Yet, as authorities in the art, Applicants have consistently argued and stipulated the patentably distinct aspects of the present invention, and have submitted a § 1.132 declaration that discusses and distinguishes Kapundu et al. *See* Christopher O. Okunji, Rule § 1.132 Declaration (June 4, 2004). Specifically, Applicants have consistently noted that Kapundu et al is strictly dependant upon the hydrolyzed seed extracts of *N. imperialis*. and the particular reasons why saponin hydrolyzation is counterintuitive and consequently counterproductive to the novel and unobvious characteristics of the present invention. To note: "the saponins were first hydrolyzed before isolation and chemical identification of the constituents...The product of hydrolysis is simpler, yielding low molecular weight compounds, less polar, less complex structurally and easy to handle... In contrast [sic] ....only naturally occurring pharmacologically active compounds were pursued...rather than hydrolyzed products....present knowledge on *N. imperialis* indicated that the major constituents of this plant are the saponins....saponin contents have been reported to vary depending on factors (discussing geographic location)...saponin distribution among the organs of a plant may vary considerably (citing as example the variation in saponin concentration in marigold flowers varies

significantly from that of the roots)....Our work on Dracaena species revealed that vary high saponin content are found mostly in the seeds." *See* Christopher O. Okunji Rule §1.132 affidavit at 6 (June 4, 2004). Note also that Applicants specifically discuss the problems associated with hydrolysis of saponins as taught by Kapundu et al. These include complications with artifact formation, low yields, low selectivity and difficulty with structure elucidation. *See* id at 8. As required by MPEP § 2112, there must be a basis in fact and/or technical reasoning to reasonably support that the allegedly inherent characteristic flows from the teachings of the prior art. No such factual basis is formulated by the Examiner because one cannot find such a teaching in Kapundu et al. Page 15 of "Kapundu et al." discloses utilizing the ground seeds of *Napoleonae imperialis* in a multistep process leading to final compound identification. These steps begin with dissolving the seeds in MeOH , Et_2OH, filtration, drying the saponin faction, redissolving again in MeOH and precipitating again with Et_2OH, followed by hydrolysis, isolation of multiple substances, acetylation, and high-pressure liquid phase chromatography. Thereafter, acid hydrolysis is required to isolate the substance and identify the sugars. *See* Kapundu et al., Translation of "New Triterpenoids from Napoleona imperialis [Triterpenoides nouveaux de Napoleonaea imperialis]," Phytochemistry 19(4) at 615 (1980 translated November 2009) . The mere recitation of a methanolic extract in a multistep isolation process does not reasonably support the Examiner's position that the allegedly inherent characteristics flows from the teachings of the prior art. To do so, would require Kapundu et al to suggest or infer the desirability of a non-hydolyzed methanolic crude extract of the powered seed of *N. imperialis* as showing efficacy as an antileishmanial composition as claimed by Applicants. Kapundu

et al does not do so, nor it can it be inferred as his intent. As stated in Applicant's § 132 Affidavit, Kapundu et al, was strictly directed to the isolation of the compounds (hence requiring the multi-step approach).

Furthermore, were the present Applicants to utilize the method of Kapundu et al, the result would be a teaching away from the present invention, as the Kapundu et al method would result in complications with artifact formation, low yields, low selectivity and difficulty with structure elucidation. *See* Christopher O. Okunji, Rule §1.132 Declaration at 8.

Additionally, as required under MPEP §707(f), the Examiner has not explicitly addressed her position in her rebuttal arguments. The Examiner states, "Applicant is invited to revisit the Non-Final Office action mail dated May 30, 2007 wherein the Examiner properly responded to each and every argument presented in Applicant's "REMARKS" filed on December 2, 200, as well as its associated 1.132 declaration filed by Christopher O. Okunji, Ph.D." *See* Examiner's Action at 4 (June 4, 2010). *See also* Examiner's Action at 7 (June 4, 2010) stating "Finally, in an Appeal Brief conference the Examiner along with Supervisory Patent Examiners Terry McKelvey and Jon Weber in attendance, upon review of the prior art made of record, it was determined that the Kapundu' reference read on the claimed invention." As the Examiner is explicitly stating that the Kapundu et al reference is being "newly applied," referring to an argument presented in a past rejection does not provide grounds to sustain the present rejection under MPEP §707(f), above, and cannot be further supported by arguing that presence of one's supervisors substantiates such a position. Such a rejection is without merit and continues to fail to meet the required burden of the inherency standard.

(C) Is the term "fractionated," as recited in claim 1, sufficiently outside of the scope of the term "fractionating" to support the Examiner's position that it provides sufficient grounds for requiring an additional search leading to the final rejection of claims 1, 11, 30 and 38 in the Examiner's Action of June 4, 2010?

Under MPEP §904, "The first search should be such that the examiner need not ordinarily make a second search of the prior art, unless necessitated by amendments to the claims by the applicant in the first reply, except to check to determine whether any reference which would appear to be substantially more pertinent than the prior art cited in the first Office action has become available subsequent to the initial prior art search. The first search should cover the invention as described and claimed, *including the inventive concepts toward which the claims appear to be directed. It should not be extended merely to add immaterial variants* (emphasis added)." Applicants initially presented the claim recitation of "fractionation" in response to the Examiner's position that "non-hydrolyzed extract" lacked antecedent basis and constituted new matter. As the discussions of direct extraction versus hydrolyzed extraction became the focal point in distinguishing the present invention from that of the prior art, Applicants utilized the term "fractionation" in their claim recitation because its definition was adequately supported by the specification. *See* Examiner's Office Action at 4 (May 30, 2007) and Applicants' Response at 10 (Nov. 30, 2007). Factually, the recitation was accepted by the Examiner as evidenced in her Office Action where she states "Claim 1 is rendered indefinite by the phrase "A biologically active extract comprising a fractionation extract" because it is not clear as to the subject matter to which Applicant intends to seek patent protection. For example, plant material may be initially extracted wither either water or methanol as a solvent in

the making of a crude plant extract followed by subjecting the crude plant extract to fractionation with one or more solvents of increasing polarity or increasing strength. It would appear that Applicant intends to direct the subject matter of the claimed invention to a biologically active extract comprising a *fractionated* (emphasis added) extract from at least one plant selected from the claim-designated Markush group recited in Claim 1." *See* Examiner's Office Action at 2 (Mar 28, 2008). The statement by the Examiner provides direct evidence that "fractionating" was understood as defined by the Applicants specification, recited in the claims and supported by MPEP§904. This is further substantiated by the statement presented in the Interview Summary Record. *See supra.* Therefore, the Applicants assert that the Examiner's statements provides implicit evidence that the amendments to the claims changing "fractionating" to "fractionated" are inventive concepts towards which the claims are directed and are also immaterial variants that would not necessitate further searching. *See Supra.*

Despite the language presented by the Examiner in the Office Action of March 28, 2008, the Examiner further contends "with regard to the "Interview Summary" mail dated July 24, 2008, the record does not indicate the term fractionated was discussed, let alone any mention of the Examiner suggesting Applicant to amend the claims to recite "fractionated." In addition to the MPEP *supra*, Applicants respectfully submit that the age of electronic searching substantially dilutes the Examiner's position that a mere tense change of a word necessitates additional searching to the level that will lead to a final rejection of the claims.

Applicants respectfully take notice of the Examiner's questioning of the veracity of Applicants' assertions with respect to the discussions made during the Telephonic

Interview. While the Interview Summary record does not indicate that the term "fractionated" was directly discussed, the Applicants and their representative, on good faith assert that such was the nature of their discussion. Furthermore, the record is clear that the Examiner provided a discussion of the term in her Office Action of March 28, 2008. *See* Examiner's Office Action of March 28, 2008 at 3 and discussion above. Additionally, in the Interview Summary Record of July 24, 2008, the Examiner states that "Amending the claims as discussed would appear to obviate the rejections of record and place Claims 1, 11, 30 and 38 in condition for allowance absent the discovery of prior art that reads on the claimed subject matter." In her Office Action of June 4, 2010, the Examiner asserts that "the record shows that Applicant proposed limiting the species recited in claim 1 to *Napoleonaea imperalis...*" intimating that the discussion of the amendment to the claims were only directed to the species limitation. However, that is not the case. Again, Applicants and their representative assert, in good faith that the discussion was also directed to a change of the term from "fractionating" to "fractionated" commensurate with the language suggested by the Examiner in her Office Action of March 28, 2008 and that the Applicants and their representative, in good faith reliance of the substance of the telephonic interview, amended claim 1 accordingly.

(D) Is the Examiner's reopening of prosecution to enter an amendment and finally rejecting the claims after submission of an Appeal Brief proper under MPEP §1207.04 when:

(i) The action is used to reapply a reference raised by the Examiner in previous office actions and omitted in subsequent Office actions;

Under MPEP §1207.04, the Examiner may reopen prosecution to enter a new ground for rejection, if the rejection was (a) necessitated by amendment or (b) based on information presented in an information disclosure statement or in a requirement for information. *See* MPEP §1207.04, 37 CFR § 1.97(c), 37 CFR §1.97(e) and MPEP §706.07(a).

In her Office Action of November 16, 2009, the Examiner reopened prosecution to enter Applicant's amendment of November 30, 2007 and newly apply Kapundu et al to reject claims 1, 11, 30 and 38 under 35 USC 102(b). *See* Examiner's Office Action of November 16, 2009 at 3. The Examiner does not note that her reasons for reopening prosecution, specifically, her reasons for newly applying her rejection of the claims under a reference already of record. No explicit statements as to MPEP§1207.04 (a) or (b) are explicitly or implicitly provided. Rather, the Examiner provides an inherency argument previously raised (these arguments are discussed above). Thus, on formal, procedural grounds, the Examiner failed to meet the requirements under MPEP §1207.04 in reopening prosecution on its merits and reopening of prosecution is improper.

(D)(ii) Does the omission of the reference in multiple subsequent Office actions and a telephonic interview indicating allowability "absent the discovery of prior art that reads on the claimed invention" act as an implied waiver of the requirement under MPEP§707.07 and MPEP § 707.07(e) (Noting All Outstanding Requirements to prevent implied waiver of the requirement):

Kapundu et al. was raised by the Examiner in her Office Action of October 25, 2002, to the parent application, then raised in the RCE non-final Office Action of May 30,

2007. However, in the subsequent Office Action of March 28, 2008, the prior art rejection of the claims were based on another reference and Kapundu et al. was not raised nor discussed. In subsequent communications from and with the Examiner, particularly the telephonic interview of July 24, 2008, there was no further mention or discussion of Kapundu et al or any other prior art reference. Nor were any mention of references made in the Advisory Action of August 21, 2008, nor Advisory Action of October 21, 2008. Applicants' response under 37 CFR §1.111 of March 16, 2010 to the Examiner's reopening of prosecution of November 16, 2009, raised this issue:

"Applicants respectfully traverse the Examiner's rejection and contend that the present Office Action is outside the scope of examination practices. While reopening of prosecution provides the Examiner a procedural mechanism to enter the claims, newly rejecting them on Kapundu et al. is questionable as the amendments to the claims were addressed by the Examiner in the Telephonic Interview and the subsequent Advisory Action, neither of which mention the Kapundu et al reference. Furthermore, Applicants note that the Examiner presents the same inherency arguments (see rebuttal arguments below) that she had presented in her Office Actions prior to March 28, 2008 and ceased to continue thereafter. Such practices do not further prosecution and fail to provide Applicants the full and bona fide examination practices to which they are entitled. Additionally, please note that the current Office Action makes no mention of the prior art rejection of the March 28, 2008 rejection. Based on the prosecution history, it is the Applicants strong position that the omission of Kapundu et al reference in the March 28, 2008 Office Action and the omission of the Okunji et al reference in the November 16, 2009 Office Action are explicit showings that both references have been overcome. This

is the standard and accepted prosecution practice before the USPTO. Thus, it is the Applicants' position that the claims are now in condition for allowance." *See* Applicants Response at 7 (March 16, 2010).

In response, the Examiner states "Applicant is mistaken. Applicant is invited to revisit the Non-final Office action mail dated May 30, 2007 wherein the Examiner properly responded to each and every argument presented in Applicant's REMARKS filed on December 20, 2006, as well as its associated 1.132 declaration filed by Christopher O. Okunji, PhD." See Examiner's Office Action of June 4, 2010 at 4.

In concurrence with the Applicants position and in light of the Examiner's admission that the reference, Kapundu et al was not raised subsequent to May 30, 2007 , Applicants contend that the omission fails to meet the requirement under MPEP §707.07 and MPEP§707.01(e), and is an implied waiver under that the Kapundu et al reference is no longer applicable and that the Examiner's reopening of prosecution was improper.

In view of the body of evidence provided above, Applicants' continue to contend that the Examiner's position is without merit. Therefore, Applicants respectfully submit that the Board overturn the rejection of claims 1, 11, 30 and 38 and hold these claims allowable.

Sincerely,

March 14, 2011
Date

Abanti A. Bhattacharyya, Esq.
Reg. No. 36,681

VIII. CLAIMS APPENDIX

The claims involved in this Appeal are as follows:

1. A biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

11. A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

30. A biologically active extract according to claim 1, wherein said solvent is methanol, wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

38. A biologically active extract according to claim 11, wherein said solvent is methanol.

IX. EVIDENCE APPENDIX

(A) Cited Case Law (in order of appearance in the Appeal Brief):

1. Sanofi-Aventis U.S. LLC v. Sandoz, Inc. 345 Fed. Appx 594 (2009)
2. In re Gleave 560 F.3d 1331 (2008); 90 USPQ.2D (BNA) 1235
3. Ex parte Gleave, No. 2007-4154 (2008); Pet. App. Lexis 33; 2008 WL 867799 (BPAI March 31, 2008).
4. In re Spada, 911 F.2d 705 (1990); 15 USPQ.2D (BNA)1655
5. In re Schoenwald 964 F.2d 1122 (1992); 22 USPQ.2D (BNA)1671
6. In re Wiggins 488 F.2d 538 (CCPA 1973); 179 USPQ (BNA)421

(B) Manual of Patent Examination Procedure Sections (in order of appearance in the Appeal Brief):

1. MPEP§2112
2. MPEP §2112.01
2. MPEP§707(f);
3. MPEP§1207.04;
4. MPEP §706.07(a)
5. MPEP §707.07
6. MPEP §707.07(e)

(C) Code of Federal Regulations (in order of appearance in the Appeal Brief):

1. 37 C.F.R. §1.97(c)

2. 37 C.F.R. §1.97(e)

(D) Prior Art Citation:

Meuza Kapundu et al.,"New Triterpenoids from *Napoleonea imperialis* [Triterpenoides nouveaux de *Napoleonaea imperialis*]," Phytochemistry, 19(4) at 615 (1980, Translation 2009).

(E) Sections of the file history (in order of appearance in the appeal brief):

(i) Applicants' Amendments and Response of:

1. March 16, 2010 (Response to a non-final rejection under 37 CFR§ 1.111)

2. July 24, 2008 (After-final Amendment)

3. May 22, 2009 (Appeal Brief)

4. June 4, 2004 (Rule 1.132 Declaration)

(ii) Examiner's Office Actions:

1. March 28, 2008 (Final rejection)

2. July 28, 2008 (Interview Summary Record of July 24, 2008)

3. August 21, 2008 and October 10, 2008 (Advisory Actions)

4. November 16, 2009 (Action reopening prosecution after Applicants filing of an Appeal Brief).

5. June 4, 2010 (Final Rejection)

X. RELATED PROCEEDINGS APPENDIX

None

2009 U.S. App. LEXIS 20294,*;345 Fed. Appx. 594

SANOFI-AVENTIS U.S. LLC, SANOFI-AVENTIS, and DEBIOPHARM S.A., Plaintiffs-Appellants, v. SANDOZ, INC., Defendant-Appellee, and TEVA PARENTERAL MEDICINES, INC., TEVA PHARMACEUTICALS USA, INC., and PHARMACHEMIE BV, Defendants-Appellees, and MAYNE PHARMA LIMITED, MAYNE PHARMA (USA) INC., HOSPIRA AUSTRALIA PTY LTD., and HOSPIRA, INC., Defendants-Appellees, and BARR LABORATORIES, INC. and PLIVA-LACHEMA A.S., Defendants-Appellees, and W.C. HERAEUS GMBH, Defendant, and APP PHARMACEUTICALS, INC. and ABRAXIS BIOSCIENCE, INC., Defendants, and ACTAVIS TOTOWA LLC, ACTAVIS, INC., and ACTAVIS GROUP HF, Defendants, and FRESENIUS KABI ONCOLOGY PLC (formerly known as Dabur Oncology plc) and FRESENIUS KABI PHARMA LIMITED (formerly known as Dabur Pharma Limited), Defendants-Appellees, and SUN PHARMACEUTICAL INDUSTRIES LTD. and CARACO PHARMACEUTICAL LABORATORIES, LTD., Defendants, and EBEWE PHARMA GES.M.B.H. NFG KG, Defendant, and MUSTAFA NEVZAT ILAC SANAYII A.S. (also known as MN Pharmaceuticals), PAR PHARMACEUTICAL COMPANIES, INC., and PAR PHARMACEUTICAL, INC., Defendants.

2009-1427, -1444

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

345 Fed. Appx. 594; 2009 U.S. App. LEXIS 20294

September 10, 2009, Decided

NOTICE:

THIS DECISION WAS ISSUED AS UNPUBLISHED OR NONPRECEDENTIAL AND MAY NOT BE CITED AS PRECEDENT. PLEASE REFER TO FEDERAL RULES OF APPELLATE PROCEDURE RULE 32.1 GOVERNING THE CITATION TO UNPUBLISHED OPINIONS.

SUBSEQUENT HISTORY: On remand at, Motion granted by, Settled by **Sanofi-Aventis U.S. LLC v. Sandoz, Inc., 2009 U.S. Dist. LEXIS 91923 (D.N.J., Oct. 2, 2009)**

PRIOR HISTORY: [*1]

On appeal from the United States District Court for the District of New Jersey in case no. 3:07-cv-02762, Judge Joel A. Pisano.
Sanofi-Aventis United States LLC v. Sandoz, Inc., 2009 U.S. Dist. LEXIS 51184 (D.N.J., June 18, 2009)

COUNSEL: **Dominick A. Conde**, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiffs-appellants. With him on the brief were **William E. Solander** and **Nina Shreve**. Of counsel was **Brian L. Klock**, of Washington, DC.

Patricia J. Thompson, Schiff Hardin LLP, of Chicago, Illinois, argued for defendant-appellee Sandoz, Inc. With her on the brief were **Douglass C. Hochstetler**, **Jason G. Harp**, and **Amethyst C. Smith**.

James F. Hurst, Winston & Strawn LLP, of Chicago, Illinois, argued for defendants-appellees Mayne Pharma Limited, et al. With him on the brief were **James M. Hilmert**, of Chicago, Illinois, **Gail J. Standish** and **Peter E. Perkowski**, of Los Angeles, California, and **Steffen N. Johnson** and **Andrew C. Nichols**, of Washington, DC.

David M. Hashmall, Goodwin Procter LLP, of New York, New York, for defendants-appellees Teva Parenteral Medicines, Inc., et al. and Barr Laboratories, Inc., et al. With him on the brief were **Frederick H. Rein** and **Keith A. Zullow**, of New York, New York, and **Henry C. Dinger**, of Boston, Massachusetts.

Steven M. Lieberman, Rothwell, Figg, [*2] Ernst & Manbeck, of Washington, DC, for defendants-appellees Fresenius Kabi Oncology PLC, et al. With him on the brief were **Minaksi Bhatt** and **Glenn E. Karta**.

JUDGES: Before LINN, PROST, and MOORE, Circuit Judges.

OPINION BY: MOORE

OPINION

MOORE, *Circuit Judge.*

Sanofi-Aventis U.S. LLC, Sanofi-Aventis, and Debiopharm S.A. (collectively, Sanofi) appeal from the district court's grant of summary judgment of noninfringement of **U.S. Patent No. 5,338,874 (the '874 patent)**. Because the district court erred in construing composition claims as product-by-process claims, we *vacate* and *remand.*

BACKGROUND

This case is on appeal from a Hatch-Waxman infringement action concerning the pharmaceutical oxaliplatin, the active ingredient in Sanofi's Eloxatin(R), approved for the treatment of colorectal cancer. A number of drug manufacturers filed Abbreviated New Drug Applications (ANDAs) seeking to market generic oxaliplatin products prior to the expiration of the **'874 patent**, which claims optically pure oxaliplatin. Sanofi sued the generic drug manufacturers (collectively defendants) for infringement under **35 U.S.C. § 271(e)(2)**, triggering a thirty-month stay of approval by the United States Food & Drug Administration (FDA) of the defendants' [*3] ANDAs pursuant to **21 U.S.C. § 355(j)(5)(B)(3)**. On June 18, 2009, the district court construed claim 1 of the **'874 patent**

as a product-by-process claim limited to "optically pure oxaliplatin that has been resolved by means of the HPLC [high performance liquid chromatography] method described in the **'874 patent** specification." **Sanofi-Aventis U.S. LLC v. Sandoz, Inc., No. 07-2762, 2009 U.S. Dist. LEXIS 51184, *28 (D.N.J. June 18, 2009)** (Claim Construction Opinion). Holding that there was no disputed issue that the defendants did not employ the HPLC method, the district court granted summary judgment of noninfringement and entered final judgment on June 30, 2008. Sanofi filed its notice of appeal on that same day. On July 10, 2009, we granted Sanofi's request to stay the judgment. On August 7, 2009, despite the stay of judgment, the FDA granted final approval of the ANDAs held by certain defendants. These defendants then launched their generic oxaliplatin products. We granted Sanofi's motion for expedited review and heard arguments on September 2, 2009.

DISCUSSION

This court reviews a grant of summary judgment *de novo.* **Immunocept, L.L.C. v. Fulbright & Jaworski, L.L.P., 504 F.3d 1281, 1286 (Fed. Cir. 2007)**. [*4] We also review claim construction *de novo.* **Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1455-56 (Fed. Cir. 1998)** (en banc). The words of a claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art in question at the time of the invention. **Phillips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005)** (en banc).

Claim 1 of the **'874 patent** recites:

1. Optically pure cis-oxalato (trans-l-1,2-cyclohexanediamine) Pt(II) having a general formula of Formula (1).

[SEE FIGURE IN ORIGINAL]

Claim 2, the only other claim at issue on appeal, depends from claim 1 and adds a melting point limitation. The district court construed the term "optically pure oxaliplatin" as "optically pure oxaliplatin that has been resolved by means of the HPLC method described in the **'874 patent** specification." n1 Claim Construction Opinion at 16.

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Mayne views this construction as an interpretation of the level of purity required by term "optically pure." Tr. of Oral Argument at 23:51-23:59, **Sanofi-Aventis U.S. LLC v. Sandoz, Inc., No. 2009-1427, 345 Fed. Appx. 594, 2009 U.S. App. LEXIS 20294 (Fed. Cir. Sept. 2, 2009)**, *available at* http://oralarguments.cafc.uscourts.gov/. However, the district court stated [*5] that it did not determine the level of purity required by the term "optically pure." *See* Claim Construction Opinion at 3 n.6. On remand, the district court may, if necessary, determine the level of purity required by the term "optically pure," by looking to "'those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean,'" including "'the words of

the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.'" **Phillips, 415 F.3d at 1314** (quoting **Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc., 381 F.3d 1111, 1116 (Fed. Cir. 2004)**).
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On appeal, Sanofi argues that the district court erred when it construed claim 1 as limited to optically pure oxaliplatin purified by the HPLC process. Sanofi argues that this claim is a composition claim and does not contain a process limitation. Defendants argue that in light of the specification and prosecution history, the district court properly limited claim 1 to optically pure oxaliplatin purified by the HPLC process.

As [*6] the district court noted, "[t]here is no dispute that nothing on the face of the claims of the **'874 patent** limits the claims to 'optically pure' oxaliplatin that is produced through the use of HPLC." Claim Construction Opinion at 16. Claim 1 is a straight forward composition claim. The district court held that the claims were nonetheless limited to oxaliplatin purified by the HPLC method in view of the specification and prosecution history. We do not agree.

We have repeatedly warned of "the danger of reading limitations from the specification into the claim." *See, e.g.*, **Phillips, 415 F.3d at 1323**. "Absent a clear disavowal or contrary definition in the specification or the prosecution history, the patentee is entitled to the full scope of its claim language." **Home Diagnostics, Inc. v. Lifescan, Inc., 381 F.3d 1352, 1358 (Fed. Cir. 2004)**. To narrow the plain language of a claim, a disclaimer must be clear and unmistakable. **Cordis Corp. v. Boston Sci. Corp., 561 F.3d 1319, 1329 (Fed. Cir. 2009)**. We see no such disclaimer in the specification or prosecution history of the **'874 patent**.

The defendants point to examples in the specification that compare the purity of oxaliplatin produced [*7] using the process discussed in a prior art reference, the Kidani process, with the purity of oxaliplatin after the HPLC process. In the "Comparative Example," the results indicate that following the Kidani process yields oxaliplatin having an optical purity of 90%. *Id.* col.7 ll.25-50, col.8 ll.13-15. Table 1 compares the purity of the samples obtained in all of the examples before and after resolution by HPLC. **'874 patent** col.8 ll.3-15. The results indicate that using HPLC optical purity was obtained. *Id.* col.8 ll.3-15. Thus, the examples illustrate how to obtain optically pure oxaliplatin. They do not clearly and unmistakably disclaim any process, and they do not justify reading a process limitation into a composition claim.

The district court relied on **Andersen Corp. v. Fiber Composites, L.L.C., 474 F.3d 1361 (Fed. Cir. 2007)**, when construing claim 1 as a product-by-process claim. In *Andersen,* this court held that claims to composite structures included a pelletizing process limitation where the patentee relied on that process both to define the invention and to distinguish the prior art. **Andersen, 474 F.3d at 1372-74**. We determined that the specification attributed the claimed physical [*8] properties to the process and that the specification indicated that the pelletizing step was *a requirement,* not a preference, of

the invention. **Id. at 1372**. We further determined that the patentee had clearly disavowed other processes during prosecution. **Id. at 1373-74**; *see also* **Chimie, 402 F.3d at 1385** (holding that "atomized precipitated silica particulates" was limited to a those silica particulates formed by the patentee's process because of an unequivocal disclaimer of other processes to overcome prior art).

By contrast, here, the patent specification and prosecution history focus on the property of the composition (optical purity) and not the process used to obtain that property. The specification defines the invention as oxaliplatin of optically high purity, not oxaliplatin prepared by the disclosed HPLC process. **'874 patent** col.2 ll.3-5 ("The present invention is cis-oxalato (trans-l-1,2-cyclohexanediamine) Pt(II) of optically high purity having general formula of Formula (1)."). The specification never asserts that HPLC is *required* to obtain optically pure oxaliplatin. It characterizes HPLC as an "illustrative method" and a "representative process" by which the claimed compound [*9] "may be prepared." *Id.* col.2 l.16, col.2 l.52, col.3 l.65. Moreover, the specification does not define the property (optical purity) by reference to the process of purification by HPLC. Thus nothing in the specification limits the invention to optically pure oxaliplatin purified using HPLC.

The prosecution history also illustrates that it is the optical purity of oxaliplatin that distinguished it from the prior art, not the process used to obtain that purity. The Examiner rejected the initially filed claims to oxaliplatin "of optically high purity" as anticipated or rendered obvious by Kidani. n2 The Examiner stated that Kidani disclosed "a single isomer [oxaliplatin] useful as an antitumor agent. Note that since the single isomer complex was prepared, the optical purity of such material is very high or almost pure isomer." In response, the applicant (Tanaka Kikinzoku Kogyo K.K., referred to herein as Sanofi) explained that it had repeated Kidani's process "using identical reactant materials and the subsequent testing thereof. . . . The resultant material was tested and found to be 90% [oxaliplatin] *not* optically pure . . . ." Sanofi explained that "[o]nly after HPLC resolution (in accordance [*10] with the teachings of the present application) was optical purity obtained." Sanofi further asserted that the products prepared using Kidani's method "do not have the presently claimed optical purity." Therefore, Sanofi argued that the claimed oxaliplatin "having high optical purity[] is not found or taught in the prior art either by inherency or by being obvious thereover." Following a telephone interview, Sanofi agreed to amend the claims to "optically pure" oxaliplatin, rather than oxaliplatin "of high optical purity." The Examiner entered the amendment and allowed the claims, stating that "[t]he Examiner agrees with applicants that Kidani et al. does not teach[] the cis-oxalato(trans-l-1,2-cyclohexanediamine)Pt(II) as an optically pure isomer. It is clear from Kidani et al. that also other isomers can be in the final product." Thus, Sanofi argued that the defining feature of the claimed oxaliplatin was its optical purity, not the HPLC process. Nothing in the prosecution history amounts to a clear and unmistakable disclaimer of optically pure oxaliplatin prepared using other (non-HPLC) processes.

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The Examiner's rejection was based on an article (Kidani et al., J. Med. Chem. 21(12) [*11] 1315-18 (1978)), which does not substantively differ from the Kidani patent.

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We conclude that the district court erred in its construction of claim 1. Claim 1 of the **'874 patent** is not limited to optically pure oxaliplatin produced by HPLC; this is a composition claim, not a product-by-process claim.

CONCLUSION

Because we conclude that the district court erred when construing the claims, we vacate the judgment of noninfringement and remand.

2009 U.S. App. LEXIS 6389,*;560 F.3d 1331;
90 U.S.P.Q.2D (BNA) 1235

IN RE MARTIN GLEAVE and MAXIM SIGNAEVSKY

2008-1453

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

560 F.3d 1331; 2009 U.S. App. LEXIS 6389; 90 U.S.P.Q.2D (BNA) 1235

March 26, 2009, Decided

PRIOR HISTORY: [*1]

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences. (Serial No. 10/346,493).

DISPOSITION:

AFFIRMED.

COUNSEL: Marina T. Larson, Marina Larson & Associates, LLC, of Dillon, Colorado, argued for appellants.

Mary L. Kelly, Associate Solicitor, Solicitor's Office. United States Patent and Trademark Office, of Arlington, Virginia, argued for the Director of the United States Patent and Trademark Office. With her on the brief was Frances M. Lynch, Associate Solicitor. Of counsel was **Raymond T. Chen**, Solicitor.

JUDGES: Before MICHEL, Chief Judge, PROST and MOORE, Circuit Judges.

OPINION BY: PROST

OPINION

PROST, *Circuit Judge*.

Martin Gleave and Maxim Signaevsky (collectively, "Gleave") filed U.S. Patent Application No. 10/346,493 ("'493 application") on January 17, 2003. The examiner rejected claims 1, 4, 15, and 18-21 as indefinite under **35 U.S.C. § 112**, P 2 and as anticipated or obvious under **35 U.S.C. § 102(b)/103(a)**. The United States Patent and Trademark Office Board of Patent Appeals and Interferences ("Board") reversed the examiner's **§ 112**, P 2 rejection and affirmed the **§ 102(b)/103(a)** rejection. **Ex parte Gleave, No. 2007-4154, 2008 Pat. App. LEXIS 33, 2008 WL 867799 (B.P.A.I. Mar.**

31, 2008). Gleave appeals the § 102/103 [*2] rejections. For the reasons set forth below, we affirm.

BACKGROUND

Gleave's '493 application is entitled "Bispecific Antisense Olignucleotides [sic] that Inhibit IGFBP-2 and IGFBP-5 and Methods of Using Same." n1 The claims are based on the understanding that certain antisense oligodeoxynucleotides can simultaneously bind to and prevent the translation of mRNA into two types of human Insulin-Dependent Growth Factor Binding Protein ("IGFBP"). The application claims antisense oligodeoxynucleotides, methods of making pharmaceutical compounds containing the oligodeoxynucleotides, and methods of treating endocrine-regulated cancers by using the oligodeoxynucleotides to prevent the formation of IGFBP-2 and IGFBP-5. The examiner rejected claims 1, 4, 15, and 18-21, all of which were composition claims directed to antisense oligodeoxynucleotides.

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We described antisense technology in greater detail in **Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir. 1999)**, and thus only give a brief overview for purposes of this opinion. In double-stranded deoxyribonucleic acid ("DNA"), only particular segments (called genes) actually encode proteins. Typically, this double-stranded DNA is "transcribed" [*3] into messenger ribonucleic acid ("mRNA"), which is complementary to one strand of the DNA. This mRNA then moves into the ribosome, where the mRNA is "translated" into a series of amino acids. Together, these amino acids form a single protein. Antisense technology is used to interrupt this process, thereby preventing certain proteins from being synthesized by the cell. Short segments of single-stranded DNA (called oligodeoxynucleotides) that are complementary to the mRNA are introduced, and physically bind to the mRNA. This prevents the mRNA from being translated into a protein. Some of these oligodeoxynucleotides are "bispecific," meaning that they can bind to mRNAs transcribed from two distinct genes and prevent the formation of both proteins.
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The Board selected claims 1 and 4 as representative. Claim 1 recites

[a] bispecific antisense oligodeoxynucleotide, wherein substantially all of the oligodeoxynucleotide is complementary to a portion of a gene encoding human IGFBP-2 and substantially all of the oligodeoxynucleotide is also complementary to a gene encoding human IGFBP-5, and wherein the oligodeoxynucleotide is of sufficient length to act as an antisense inhibitor of human IGFBP-2 [*4] and human IGFBP-5.Claim 4 recites "[t]he antisense oligodeoxynucleotide according to claim 1, wherein the oligodeoxynucleotide consists essentially of a series of bases as set forth in any of Seq. ID. Nos. 3 through 7." Those sequences range from eighteen to twenty-two DNA bases in length. Before the examiner, Gleave elected Sequence No. 5, a twenty-base oligodeoxynucleotide. The specification notes that the invention does not exclude "minor

modifications in sequence, such as the addition of one or two terminal bases, or single base substitutions which might depart from perfect complementarity."

The examiner initially rejected the claims over the published PCT application 00/78341 of Wraight et al. ("Wraight"). In Wraight, the applicants listed every fifteen-base-long *sense* oligodeoxynucleotide in the IGFBP-2 gene. The list includes more than 1400 sequences. Wraight also disclosed the general concepts that antisense oligonucleotides are preferably between fifteen and twenty-five bases in length, and that some antisense oligonucleotides may be bispecific (i.e., capable of inhibiting "an IGFBP such as IGFBP-2 and/or IGFBP-3"). Finally, Wraight states that "[a]ntisense oligonucleotides [*5] to IGFBP-2 may be selected from molecules capable of interacting with one or more" of the sense oligonucleotides described in the long list.

The Board found that to anticipate claim 1, the prior art had to describe an oligodeoxynucleotide of sufficient length to act as an antisense inhibitor to human IGFBP-2 and IGFBP-5, and substantially all of the oligodeoxynucleotide had to be complementary to a portion of the gene encoding human IGFBP-2 and complementary to the gene encoding human IGFBP-5. The Board found that Wraight satisfied these requirements and anticipated the claims. The Board also affirmed the **§ 103** rejection.

The issue presented on appeal, therefore, is whether a reference that lists every fifteen-base sense oligodeoxynucleotide in a known nucleic acid sequence anticipates or renders obvious claims to specific antisense sequences having particular properties. We have jurisdiction over the appeal under **28 U.S.C. § 1295(a)(4)(A)**.

DISCUSSION

As an initial matter, the parties disagree over the proper standard of review. Under **35 U.S.C. § 102(b)**, a patent applicant cannot receive a patent if the invention was "described in a printed publication in this or a foreign country . . [*6] . more than one year prior to the date of the application for patent in the United States." Gleave claims that the issue at hand is "in essence" one of statutory construction (i.e., what a reference must disclose to "describe" an invention under **§ 102(b)**); thus, Gleave argues we should review the Board's decision de novo. n2 Yet Gleave has not unearthed for us some previously hidden requirement for a reference to anticipate an invention under **§ 102(b)**.

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The PTO argued that Gleave "waived review of the legal issue he now asserts by failing to raise it before the Board." We disagree. The entire thrust of Gleave's brief on appeal to the Board was the "significance" of Wraight's disclosure in an anticipation analysis. Gleave argued this position as early as his first office action response on March 12, 2005.
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A reference is anticipatory under **§ 102(b)** when it satisfies particular requirements. First, the reference must disclose each and every element of the claimed invention, whether it

does so explicitly or inherently. **Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1375 (Fed. Cir. 2006)**. While those elements must be "arranged or combined in the same way as in the claim," [*7] **Net MoneyIN, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1370 (Fed. Cir. 2008)**, the reference need not satisfy an *ipsissimis verbis* test, **In re Bond, 910 F.2d 831, 832-33 (Fed. Cir. 1990)**. Second, the reference must "enable one of ordinary skill in the art to make the invention without undue experimentation." **Impax Labs., Inc. v. Aventis Pharms. Inc., 545 F.3d 1312, 1314 (Fed. Cir. 2008)**; *see* **In re LeGrice, 301 F.2d 929, 940-44, 49 C.C.P.A. 1124, 1962 Dec. Comm'r Pat. 707 (CCPA 1962)**. As long as the reference discloses all of the claim limitations and enables the "subject matter that falls within the scope of the claims at issue," the reference anticipates--no "actual creation or reduction to practice" is required. **Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1380-81 (Fed. Cir. 2003)**; *see* **In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985)**. This is so despite the fact that the description provided in the anticipating reference might not otherwise entitle its author to a patent. *See* **Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1562 (Fed. Cir. 1991)** (discussing the "distinction between a written description adequate to *support* a claim under **§ 112** and a written description sufficient to *anticipate* its subject matter under **§ 102(b)**").

As [*8] this summary makes clear, the outcome in this case depends largely on the facts. After all, anticipation is a question of fact, including whether an element is inherent in the prior art. **Eli Lilly, 471 F.3d at 1375**. And as with **35 U.S.C. § 112**, "[w]hether a prior art reference is enabling is a question of law based upon underlying factual findings." **Minn. Mining & Mfg. Co. v. Chemque, Inc., 303 F.3d 1294, 1301 (Fed. Cir. 2002)**. We review the Board's factual determinations for substantial evidence. **In re Gartside, 203 F.3d 1305, 1315 (Fed. Cir. 2000)**. The Board's legal conclusions, on the other hand, we review de novo. **In re Elsner, 381 F.3d 1125, 1127 (Fed. Cir. 2004)**.

A

Gleave frames the issue presented for review as "the meaning of the term 'described' in **35 U.S.C. § 102(b)** and the type of disclosure that is therefore required for a reference to be anticipatory." Specifically, Gleave claims that "Wraight does not describe any particular individual antisense species," because Wraight merely gives the public "ink, formed into strings of letters, without inventive thought and without placing the public in possession of anything new. There is no guidance to make particular selections, [*9] and no understanding of which of the targets would be useful, and what the properties of the related antisense would be."

We have at times framed the issue of enablement under **§ 102** as a question of whether one of ordinary skill in the art would know how to "make *and use*" the invention based on the reference's disclosure. *See, e.g.*, **Impax Labs., Inc. v. Aventis Pharms., Inc., 468 F.3d 1366, 1381 (Fed. Cir. 2006)** ("[A] prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art."); **Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1374 (Fed. Cir. 2001)** ("To anticipate, the reference must also enable one of skill in the art to make and use the claimed invention."). Taken out of context, these formulations of our **§ 102** enablement

standard arguably support a use or utility requirement divorced from any "make" requirement. A thorough reading of our case law, however, makes clear that a reference need disclose no independent use or utility to anticipate a claim under § 102. *E.g.*, **Novo Nordisk Pharm., Inc. v. Bio-Tech. Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005)** ("The standard for enablement of a prior art reference [*10] for purposes of anticipation under [§] 102 differs from the enablement standard under 35 U.S.C. § 112."); **Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1326 (Fed. Cir. 2005)** ("[A] prior art reference need not demonstrate utility in order to serve as an anticipating reference under [§] 102."); **In re Hafner, 410 F.2d 1403, 1405, 56 C.C.P.A. 1424 (CCPA 1969)** ("[Section] 112 provides that the specification must enable one skilled in the art to 'use' the invention whereas § 102 makes no such requirement as to an anticipatory disclosure.").

The confusion stems from the fact that where a method claim is at issue, it is a largely meaningless formulation of the standard to require a reference to disclose how to "make" that method in order to anticipate. For method claims, the "make" requirement *becomes*, in effect, a "use" requirement. The only way one can show that a reference enables the method is to show that a person of ordinary skill would know how to use--in other words, to practice or to carry out--the method in light of the reference. This does not mean, however, that the prior art reference must demonstrate the invention's *utility*. For instance, in the context of a claimed method for treating [*11] a disease, a prior art reference need not disclose "proof of efficacy" to anticipate the claim. **Impax Labs., 545 F.3d at 1315**; **Rasmusson, 413 F.3d at 1326**. Gleave's claims are to compositions of matter--oligonucleotides--and therefore a reference satisfies the enablement requirement of **§ 102(b)** by showing that one of skill in the art would know how to make the relevant sequences disclosed in Wraight. Thus, the fact that Wraight provides "no understanding of which of the targets would be useful" is of no import, because Gleave admits that it is well within the skill of an ordinary person in the art to make any oligodeoxynucleotide sequence. *See* Appellant's Br. 10. As such, Wraight is an enabling disclosure sufficient to anticipate Gleave's invention under **§ 102(b)**.

Gleave also points out that "[n]o example of an actual antisense oligonucleotide complementary to a sequence on [Wraight's] list is shown to have antisense activity." *Id.* at 4. We need not address any inherency issues, however, because the simple fact is that *Gleave's* composition claims do not require antisense activity either. The claims at issue merely require the oligodeoxynucleotides to be "of sufficient length to act [*12] as an antisense inhibitor of human IGFBP-2 and human IGFBP-5." *See* Oral Arg. at 1:18, *available* at http://oralarguments.cafc.uscourts.gov/mp3/2008-1453.mp3 (Judge Prost: "I'm a little confused by this, and I guess turning to the language in claim 1, doesn't it just disclose an oligo 'of sufficient length to act as an antisense inhibitor?' And I'm not seeing where the language requires that the oligo actually acts as an antisense inhibitor." Gleave's counsel: "No, it doesn't."). As explained above, evidence as to whether particular compounds work for their intended purpose is irrelevant to our **§ 102(b)** analysis. Certainly where the claims themselves do not require a particular activity, we have no call to require something more from the anticipating reference.

B

At its core, Gleave's primary argument is rooted in policy:

Where the allegedly anticipatory disclosure is only a small part of a much larger and exhaustive listing and there is no basis in the art for selecting some individual members of the listing over others, what is actually described and what is actually disclosed to the public is no more than the generic concept underlying the list.Appellant's Br. 6. In other words, Gleave [*13] argues that we should collapse the distinction between a list and a genus disclosure. *See* Oral Arg. at 4:42, *available at* http://oralarguments.cafc.uscourts.gov/mp3/2008-1453.mp3 (Judge Moore: "I understand what you're saying--from a policy perspective, you'd like us to say when a list gets long enough, you ought to treat them the same." Gleave's counsel: "No, I'm not even saying when a list gets long enough. I'm saying when a list provides no more information to an inve--to the public than the generic statement would.") If we did, the argument goes, then we would recognize that Wraight simply provides a "long winded form of a statement that 'you could make antisense that targets IGFBP-2.'"

Gleave also cites *In re Wiggins* for the proposition that a list of compounds, "without any direction as to selection among the targets, is not a description of any one of these targets." Gleave urges us to find that *Wiggins* "clearly expressed the policy concerns which this case exemplifies, that giving prior art effect to individual members of lists of thousands of theoretically possible compounds would be contrary to the purpose sought to be effectuated by the patent law." Reply Br. 7-8 (citing **In re Wiggins, 488 F.2d 538, 543 (CCPA 1973)** [*14] (quotations omitted)).

In *Wiggins*, the Court of Customs and Patent Appeals stated:

In our view, [the alleged anticipatory reference's] listing of the compounds by name constituted nothing more than speculation about their *potential or theoretical* existence. The mere naming of a compound in a reference, without more, cannot constitute a description of the compound, *particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference*.

If we were to hold otherwise, lists of thousands of *theoretically possible* compounds could be generated and published which, assuming it would be within the level of skill in the art to make them, would bar a patent to the actual discoverer of a named compound no matter how beneficial to mankind it might be.**488 F.2d at 543** (emphases added).

Gleave reads **Wiggins** to suggest that a description of a compound cannot be anticipatory where it appears in a long list of other compounds. That conclusion, however, ignores the facts at issue in that case. Contrary to Gleave's representations, no evidence existed that a person of ordinary skill in the art could make [*15] the compounds disclosed in the alleged anticipatory reference at the time of disclosure. The reference, published in 1957, mentioned by name two compounds that fell within the scope of Wiggins's claims. But

the reference also noted that the synthesis of these compounds had been unsuccessful; further, the only publication of record that disclosed a method of making the compounds was not published until two years later. In short, the reference was not an enabling reference--no person of ordinary skill in the art could make the claimed invention in 1957. n3

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It is true that "[e]nablement of an anticipatory reference may be demonstrated by a later reference." **Bristol-Myers Squibb, 246 F.3d at 1379**. But in *Wiggins*, our predecessor court did not elect to decide the case on this ground. **488 F.2d at 543 n.4** ("We do not mean to suggest that we have actually evaluated the process taught by [the later reference] and concluded that it could be used to prepare the claimed compounds. As this is irrelevant to our decision, we express no opinion on this point.").
- - - - - - - - - - - - End Footnotes- - - - - - - - - - - - -

The *Wiggins* court stated that "[t]he [*16] mere naming of a compound in a reference, without more, cannot constitute a description of the compound." **488 F.2d at 543**. We agree. The mere naming of a *theoretical* compound, *without more*, cannot constitute a description under **§ 102(b)**. "Without more" is the key phrase, and read as a whole *Wiggins* makes clear just what this something "more" is--a person of ordinary skill in the art's ability to make the claimed compound. *See also* **Donohue, 766 F.2d at 533-34**; **In re Samour, 571 F.2d 559, 562-64 (CCPA 1978)**; **In re Brown, 329 F.2d 1006, 1009-10, 51 C.C.P.A. 1254, 1964 Dec. Comm'r Pat. 548 (CCPA 1964)** (discussing **In re Von Bramer, 127 F.2d 149, 29 C.C.P.A. 1018, 1942 Dec. Comm'r Pat. 462 (CCPA 1942)**). This point is underscored by the excerpt: not once, not twice, but three times the court pointed out that its discussion was in the context of "potential or theoretical" compounds. That was the issue presented to the court, and that was the issue it decided.

For the purposes of whether they are anticipatory, lists and genera are often treated differently under our case law. *Compare* **Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1376 (Fed. Cir. 2005)** (rejecting "the notion that [a compound] cannot anticipate because it appears without special emphasis in a longer list") *with* **Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006)** [*17] ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."). This distinction collapses when the class of compounds that falls within the genus is so limited that a person of ordinary skill in the art can "at once envisage each member of this limited class." **Eli Lilly, 471 F.3d at 1376**. In that limited circumstance, a reference describing the genus anticipates every species within the genus. *See* **Perricone, 432 F.3d at 1377**. In this case, Gleave's arguments fail for two reasons. First, Wraight expressly lists every possible fifteen-base-long oligodeoxynucleotide sequence in IGFBP-2, and under our precedent, this list anticipates Gleave's claims. Second, even if we were to accept Gleave's invitation to treat Wraight as equivalent to the statement that one "could make antisense that targets IGFBP-2," n4 which we decline to do, a person of ordinary skill in the art equipped with an IGFBP sequence is admittedly capable of envisioning how to make any antisense sequence.

Thus, even if we were to adopt Gleave's policy position, Gleave's claims would not be entitled to a patent over Wraight.

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We note [*18] that this is not the full extent of Wraight's disclosure. *See supra* at 3.
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The rest of Gleave's arguments fare no better. For instance, Gleave protests that Wraight "does not show that sequences antisense to any of the sequences in this list were actually made and tested." As we have already made clear, it is not "necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement." **Donohue, 766 F.2d at 533**. In light of the foregoing, we agree with the Board's conclusion that Gleave's claims are invalid as anticipated by Wraight.

CONCLUSION

In sum, "[t]he discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition." **In re Spada, 911 F.2d 705, 708 (Fed. Cir. 1990)**. The compositions described in the '493 application are simply not new--they were described in Wraight's enabling disclosure. As we explained in *In re Schoenwald*, Gleave's contribution, at best, is "finding a use for the compound, not discovering the compound itself." **964 F.2d 1122, 1124 (Fed. Cir. 1992)**. If the *use* Gleave discovered [*19] is new, he will be able to patent that method of use--"any more would be a gratuity." *Id.* Therefore, we affirm the Board's rejection of claims 1, 4, 15, and 18-21 of the '493 application under **§ 102(b)**. We need not reach the **§ 103** obviousness rejection.

AFFIRMED

Board of Patent Appeals and Interferences

2008 Pat. App. LEXIS 33

March 31, 2008, Decided

CORE TERMS: antisense, sequence, oligonucleotide, complementary, oligodeoxynucleotide, gene, encoding, specification, invention, inhibitor, anticipation, anticipated, bispecific, effective, obviousness, modifications, substitutions, disclosure, compound, consisting, anticipate, molecule, indefinite, skill, subject matter, complementarity, composition, perfect, elected, skilled

[*1]

Before, DEMETRA J. MILLS, LORA M. GREEN, and RICHARD M. LEBOVITZ, Administrative Patent Judges.

OPINIONBY: MILLS

OPINION:

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims as being anticipated and/or obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

The following claims are representative.

1. A bispecific antisense oligodeoxynucleotide, wherein substantially all of the oligodeoxynucleotide is complementary to a portion of a gene encoding human IGFBP-2 and substantially all of the oligodeoxynucleotide is also complementary to a gene encoding human IGFBP-5, and wherein the oligodeoxynucleotide is of sufficient length to act as an antisense inhibitor of human IGFBP-2 and human IGFBP-5.

4. The antisense oligodeoxynucleotide according to claim 1, wherein the oligodeoxynucleotide consists essentially of a series of bases as set forth in any of Seq. ID. Nos. 3 through 7.

Cited Reference by the Examiner:

Wraight et al. WO 07/78341 A1 December 28, 2000

References cited by Appellants:

Agrawal et al., "Antisense therapeutics: [*2] it is as simple as complementary base recognition?", Reviews, Molecular Medicine Today, 61: 72-81 (2000).

Vickers et al., "Effects of RNA secondary structure on cellular antisense activity," Nucleic Acids Research, 28 (6): 1340-1347 (2000).

Branch, "A good antisense molecule is hard to find," TIBS Talking Point 23: 45-50 (Feb. 1998).

Grounds of Rejection

1. Claims 1, 4, 15 and 18-21 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite (Ans. 3).

2. Claims 1, 4, 15 and 18-21 stand rejected under 35 U.S.C. § 102(b)/103(a) as anticipated or obvious in view of Wraight (Ans. 4).

DISCUSSION

Background

This present application relates to bispecific antisense olignucleotides that inhibit insulin-like growth factors, IGFBP-2 and IGFBP-5, and methods of using the oligonucleotides in the treatment of endocrine-regulated tumors (for example, breast, prostate, ovarian and colon cancers). (Spec.1.)

According to the Examiner, the "elected invention is a bispecific oligonucleotide and pharmaceutical compositions comprising the oligonucleotide. The specific oligonucleotide sequence elected [*3] is SEQ ID NO:5. See Appellants' response filed 8/16/04 to the restriction requirement of 7/20/04." (Ans. 4.)

1. Claims 1, 4, 15 and 18-21 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite.

The Examiner argues these claims are indefinite because it is unclear what is intended by the phrase "substantially all of the oligodeoxynucleotide" as recited in claims 1 and 15 (Ans. 3).

The Examiner quotes (Ans. 3) from the Specification at page 4, lines 17-26:

The present invention provides bispecific antisense oligonucleotides which consist essentially of a sequence of bases that is complementary to portions of both the gene

encoding IGFBP-2 and the gene encoding IGFBP-5, and that is sufficient length to act as an inhibitor of the effective amount of IGFBP-2 and IGFBP-5 (in general at least 15 bases). As used in the specification and claims of this application, this language means that substantially all of the antisense oligonucleotide is complementary to a portion of each gene sequence. The invention does not, however, exclude minor modifications in sequence, such as the addition of one or two terminal bases, or single base substitutions [*4] which might depart from perfect complementarity but which still function as an inhibitor of the effective amount of IGFBP-2 and IGFBP-5. Based on this passage it is unclear how many single base substitutions are allowed within the metes and bounds of the claim.

(Ans. 3)

Appellants contend that "one skilled in the art can know whether a given composition that may have substitutions falls within the scope of the claims, by observing whether or not it inhibits both IGFBP-2 and IGFBP-5." (Reply Br. 2.)

Definiteness is determined from the perspective of a person of skill in the relevant art. See Union Pacific Resources Co. v. Chesapeake Energy Corp., 236 F.3d 684, 692 (Fed. Cir. 2001) ("The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification.); Miles Laboratories Inc. v. Shandon Inc., 997 F.2d 870, 875 (Fed. Cir. 1993) ("The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification.").

In the section quoted by the Examiner, the [*5] Specification states that "substantially all of the antisense oligonucleotide is complementary to a portion of each gene sequence." (Spec. 4.) "The invention does not, however, exclude minor modifications in sequence, such as the addition of one or two terminal bases, or single base substitutions which might depart from perfect complementarity but which still function as an inhibitor of the effective amount of IGFBP-2 and IGFBP-5." (Spec. 4.)

In our view, the Specification defines to one of ordinary skill in the art that what is meant by the term "substantially all" is that the sequence may contain minor modifications which still allow the sequence to function as an inhibitor of the effective amount of IGFBP-2 and IGFBP-5. Such modifications are stated to include single base substitutions which might depart from perfect complementarity. Thus, we find that the language "substantially all" as interpreted by one of ordinary skill in the art defines the metes and bounds of the claim. The rejection is reversed.

The Examiner also rejects claims 4, 18, 20 and 21 as indefinite in their recitation of "consists essentially of" and argues it is "unclear how this limits the claimed subject matter." [*6] (Ans 3.)

The Examiner contends that,

[g]enerally "consists essentially of" is used in the context of composition claims in which it is clear that the invention must contain certain essential elements, and may also contain other optional elements. However, in this case, the claimed invention is not a composition, it is a molecule. The specification does not make clear what are the essential physical characteristics of the molecule that are required to perform the required function of acting as an antisense inhibitor. Also it is not clear if claims 18, 20, and 21 require all of SEQ ID NO:5, or just some essential fragment of SEQ ID NO:5.

(Ans.)

We do not find the Examiner has set forth a prima facie case of indefiniteness. Contrary to the Examiner's contention, the Specification, page 4, does provide a definition of the meaning of "consisting essentially of" in the context of the present claims. The Specification states that, as used in the Specification and claims of this application, the language "consisting essentially of"

means that substantially all of the antisense oligonucleotide is complementary to a portion of each gene sequence. The invention does not, however, exclude [*7] minor modifications in sequence, such as the addition of one or two terminal bases, or single base substitutions which might depart from perfect complementarity but which still function as an inhibitor of the effective amount of IGFBP-2 and IGFBP-5.

(Spec. 4.)

The transitional phrase "consisting essentially" of limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52 (CCPA 1976). The basic and novel characteristics of the claimed antisense sequence are that they inhibit IGFBP-2 and IGFBP-5, including sequences with minor modifications. We find that the definition provided in the Specification is sufficient to describe the basic and novel characteristics of the antisense sequences claimed. The rejection for indefiniteness is reversed.

2. Claims 1, 4, 15 and 18-21 stand rejected under 35 U.S.C. § 102(b)/103(a) as anticipated or obvious in view of Wraight. We select claim 1 as representative of the rejection before us since Appellants have not separately argued [*8] the claims. 37 C.F.R. 41.37(c)(1)(vii).

Claim Interpretation

During ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. In re Zletz, 893 F.2d 319, 321 (Fed. Cir. 1989).

Claim 1 recites a "bispecific antisense oligodeoxynucleotide, wherein substantially all of the oligodeoxynucleotide is complementary to a portion of a gene encoding human IGFBP-2 and substantially all of the oligodeoxynucleotide is also complementary to a portion of a gene encoding human IGFBP-5, and wherein the oligodeoxynucleotide is of sufficient length to act as an antisense inhibitor of human IGFBP-2 and human IGFBP-5." Thus, to anticipate claim 1, it must be established that the prior art describes an oligodeoxynucleotide of sufficient length to act as an antisense inhibitor of human IGFBP-2 and human IGFBP-5 and that substantially all of the oligodeoxynucleotide is complementary to a portion of a gene encoding human IGFBP-2 and substantially all of the oligodeoxynucleotide is also complementary to a gene encoding human IGFBP-5. The elected invention is directed to SEQ [*9] ID NO:5. (See, e.g. claim 4.) Thus, because of Appellants' use of the claim language in claim 1 upon which claim 4 depends of "consisting essentially of" and "substantially all," even though SEQ ID NO:5 is 20 bases in length, a nucleotide need not be 20 bases in length in order to anticipate the oligodeoxynucleotide of claim 1.

The Examiner finds that:

SEQ ID NO:5 is 20 bases in length.

Wraight taught inhibition of human insulin-like growth factor binding protein 2 (IGFBP2) through administration of antisense oligonucleotides. See page 23, lines 7-14. More specifically, Wraight disclosed that "[a]ntisense oligonucleotides to IGFBP2 may be selected from molecules capable of interacting with one or more of" a list of sense oligonucleotides, and the list contains six different 15mer targets that are complementary over their whole length to instant SEQ ID NO:5. See page 34, lines 1 and 2, and page 36, column 2, lines 25-30. Wraight also disclosed that antisense oligonucleotides should be 15-25 bases in length. See page 23, lines 19-26. Thus Wraight fairly disclosed at least six oligonucleotides comprising 15 bases of instant SEQ ID NO:5, and so taught at least 6 antisense oligonucleotides [*10] consisting essentially of a series of bases set forth in SEQ ID NO:5. ... Because the antisense oligonucleotides of Wraight meet all the structural limitations of the instant claims, they comprise a bispecific antisense oligonucleotide that consists essentially of a sequence of bases that is complementary to portions of both the human gene encoding IGFBP-2 and the human gene encoding IGFBP-5 as set forth in SEQ ID NO: 5.

(Ans. 4-5.)

Appellants contend that, "[n]o example of an actual antisense oligonucleotide complementary to a sequence ... is shown to have antisense activity with respect to

IGFBP-2." (Appeal Br. 4.) Appellants further argue that the listing of antisense nucleotides in Wraight

do not convey any more information than the simple sequence listing because they do not provide any information about the properties of the oligonucleotide represented by an individual groupings of letters, nor do they provide any guidance as to which of the numerous sequences may actually be effective for the asserted utility as antisense.

(Appeal Br. 4-5.)

Appellants argue that the disclosure of Wraight is not anticipatory for the claimed antisense sequences and that their position [*11] is supported by the case law of In re Arkley, 455 F.2d 586, 587 (CCPA 1972) and Ex parte A, 17 USPQ2d 1716 (BPAI 1990). (Appeal Br. 5.) We are not persuaded by Appellants' arguments, and find that the claimed antisense sequence is anticipated by the antisense sequences disclosed in Wraight.

The standard under § 102 is one of strict identity. "Under 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim." Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997). "Every element of the claimed invention must be literally present, arranged as in the claim." Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 1236 (Fed. Cir. 1989).

All of the six sequences of Wraight cited by the Examiner are complementary to a portion of a gene encoding human IGFBP-2 and to a portion of a gene encoding human IGFBP-5. The oligodeoxynucleotides are of sufficient length to act as an antisense inhibitor of human IGFBP-2 and human IGFBP-5. Furthermore, the oligonucleotide [*12] sequences disclosed in Wraight are complementary to a portion of a gene encoding IGFBP-2 and IGFBP-5 which "consist essentially of" and "substantially all" of the bases as set forth in SEQ. ID. No. 5. Thus, the six sequences in Wraight comprising 15 bases of instant SEQ ID NO:5 anticipate the oligodeoxynucleotide of claim 1.

Nor do we find the case law of In re Arkley to be on point. In In re Arkley the claims to a cephaloridine were rejected as anticipated over Flynn. The claims were not rejected on the basis of obviousness over Flynn. The Court held that an anticipation rejection under 35 U.S.C. § 102 is proper

only when the claimed subject matter is identically disclosed or described in "the prior art." Thus, for the instant rejection under 35 U.S.C. 102(e) to have been proper, the Flynn reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference. Such picking and choosing may be [*13] entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the similarity

of the subject matter which he claims to the prior art, but it has no place in the making of a 102, anticipation rejection.

The Court found the anticipation rejection improper because it attempted to arrive at anticipation by combining the disclosures in examples 4 and 10 in the Flynn patent. The facts of the present case can be distinguished from Arkley. The Examiner in the present case has not combined separate disclosures from Wraight, but has found that at least 6 antisense sequences (15mers) disclosed in Wraight are complementary to a portion of the 20mer sequence of SEQ ID NO:5 in the pending claims. Thus the antisense sequences of Wraight anticipate claims 1 and 4, as elected.

As to Ex parte A, 17 USPQ2d 1716 (BPAI 1990), in that case the Board found 22 compounds provided in a list in the cited reference, anticipated the claimed compound. The Board also indicated that, "[e]ven if the number of compounds disclosed in the reference [*14] were several orders of magnitude greater, we would come to the same conclusion." (Id at 1718.) We similarly find that the list of antisense sequences disclosed in Wraight, describes the bispecific antisense oligodeoxynucleotide of the pending claims which is complementary to a portion of SEQ ID NO:5.

Appellants further put forth several references, Agrawal, Branch and Vickers to support their position that one of ordinary skill in the art would not expect all or even most of the sequences disclosed in Wraight to be operative as antisense sequences. (Reply Br. 3-4.) Thus, Appellants essentially argue that Wraight is a non-enabling disclosure of the claimed antisense sequence.

Each reference cited by Appellants evidences some problem in the art associated with antisense technology. Agrawal evidences that "[a]ntisense technology has been hampered to some extent by limited knowledge as to the base-pairing accessibility of mRNA target sites in vivo. Although a number of models that predict mRNA folding are available, their usefulness for predicting the most plausible in vivo structure is limited." (Agrawal, 76-77.) Vickers shows that "for an antisense oligonucleotide [*15] to be effective, the complementary target sequence must be available for hybridization. This is not always the case as the RNA target is not single-stranded random coil but contains secondary and tertiary structures that have been show to affect the affinity and rate of oligonucleotide hybridization." (Vickers, 1340.) Branch discloses that antisense molecules are far more difficult to produce than originally anticipated and a wide variety of unexpected non-antisense effects have come to light. (Branch, abstract.) While the conclusions in the references put forth may be true of the antisense technology, they do not negate the plain fact that Wraight discloses (enables) six sequences that are complementary to a portion of SEQ ID NO:5, meeting all the limitations of the oligodeoxynucleotide claimed in claim 1. For this reason, we are not persuaded by Appellant's arguments.

Anticipation being the epitome of obviousness, we also affirm the rejection of the claims under 35 U.S.C. § 103 as being obvious in view of Wraight. In re Fracalossi, 681 F.2d 792, 794 (CCPA 1982).

We find that the Examiner has established a prima [*16] facie case of anticipation/obviousness of the claimed subject matter that has not been adequately rebutted by Appellants. The rejection is affirmed.

SUMMARY

The rejections of the claims for indefiniteness are reversed. The rejection of the claims for anticipation/obviousness are affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

IN RE LONNIE T. SPADA and JOSEPH J. WILCZYNSKI

No. 90-1109

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

911 F.2d 705; 1990 U.S. App. LEXIS 13674; 15 U.S.P.Q.2D (BNA) 1655

August 10, 1990, Decided

PRIOR HISTORY: [**1] Appealed from United States Patent and Trademark Office Board of Patent Appeals and Interferences.

DISPOSITION: AFFIRMED.

CASE SUMMARY

PROCEDURAL POSTURE: Appellants challenged a decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences, rejecting all of the claims at issue of their patent application under 35 U.S.C.S. §§ 102 and 103.

OVERVIEW: The Patent and Trademark Office rejected all of the claims at issue of appellants' patent application under 35 U.S.C.S. §§ 102 and 103. The appellate court affirmed, holding that a prima facie case of anticipation was made in view of an earlier reference even though the properties described in the earlier reference were included as express limitations in appellants' claims. The court said that appellant was reasonably required to show that his claims were different from those described in the earlier reference and did not meet the burden by simply including the asserted different properties in his claims. The compositions were not novel and were not rendered patentable by the recitation of certain properties, whether or not those properties were shown or suggested in the prior art.

OUTCOME: The appellate court affirmed an order rejecting the claims at issue of appellants' patent application where it determined that a prima facie case of anticipation was made in view of an earlier reference even though the properties described in the earlier reference were included as express limitations in appellants' claims.

CORE TERMS: polymer, composition, monomer, invention, acrylate, patent, prima facie case, adhesive, novelty, latex, tacky, molar, prior art, anticipation, disclosure, acrylic acid, polymerizable, olefinically, temperature, unsaturated, comprising,

carboxylic, functional, butyl, pressure-sensitive, anticipated, chemical, novel, acid ester, normally

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Patent Law > Anticipation & Novelty > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview

HN1 The hybrid rejection under 35 U.S.C.S. §§ 102 or 103 is made on the theory that if the claimed subject matter is novel, i.e. not anticipated, in terms of 35 U.S.C.S. § 102, then it is obvious under 35 U.S.C.S. § 103.

Patent Law > U.S. Patent & Trademark Office Proceedings > Examinations > General Overview

HN2 The Patent and Trademark Office's practice of basing rejections on 35 U.S.C.S. § 102 or 35 U.S.C.S. § 103 in the alternative is acceptable provided that the appellant is fully apprised of all the grounds of rejection.

Patent Law > Anticipation & Novelty > General Overview
Patent Law > Nonobviousness > Evidence & Procedure > Prima Facie Obviousness

HN3 A prima facie case of anticipation is a procedural tool which, as used in patent examination (as by courts in general), means not only that the evidence of the prior art would reasonably allow the conclusion the examiner seeks, but also that the prior art compels such a conclusion if the applicant produces no evidence or argument to rebut it. Upon rebuttal, the decision is made on the entirety of the record.

Patent Law > Anticipation & Novelty > General Overview

HN4 Rejection for anticipation or lack of novelty requires, as the first step in the inquiry, that all the elements of the claimed invention be described in a single reference. Further, the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it.

Patent Law > Anticipation & Novelty > General Overview
Patent Law > Nonobviousness > Elements & Tests > Prior Art
Patent Law > Ownership > Patents as Property

HN5 The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition. Thus, the initial inquiry is to the novelty of the composition.

Patent Law > Anticipation & Novelty > General Overview

HN6 Products of identical chemical composition cannot have mutually exclusive properties.

Patent Law > U.S. Patent & Trademark Office Proceedings > Examinations > General Overview

HN7 In response to the Patent and Trademark Office's (PTO) asserted prima facie case the applicant may argue that the inference of lack of novelty was not properly drawn, for example if the PTO did not correctly apply or understand the subject matter of the reference, or if the PTO drew unwarranted conclusions therefrom. However, when the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.

Patent Law > Anticipation & Novelty > General Overview

HN8 An inventor is not required to understand how or why an invention works.

Patent Law > Anticipation & Novelty > General Overview

HN9 Newly discovered properties can be the basis of claims to novel polymers.

Patent Law > Anticipation & Novelty > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview

HN10 Without novelty, evidence of unobviousness is superfluous.

Patent Law > Anticipation & Novelty > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview

HN11 Discovery of an unobvious property and use does not overcome the statutory restraint of 35 U.S.C.S. § 102 when the claimed composition is known.

Patent Law > Anticipation & Novelty > General Overview

HN12 When claimed compositions are not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.

COUNSEL: James H. Laughlin, Jr., Benoit, Smith & Laughlin, of Arlington, Virginia, argued for Appellant. With him on the brief was Michael H. Laird, Unocal Corporation, Brea, California, of Counsel.

John H. Raubitschek, Associate Solicitor, Office of the Solicitor, of Arlington, Virginia, argued for Appellee. With him on the brief was Fred E. McKelvey, Solicitor.

JUDGES: Newman and Mayer, Circuit Judges, and Garrett E. Brown, District Judge. [*]

[*] Judge Garrett E. Brown, Jr., United States District Court for the District of New Jersey, sitting by designation.

OPINION BY: NEWMAN

OPINION

[*706] NEWMAN, Circuit Judge.

The decision of the United States Patent and Trademark Office (the PTO) Board of Patent Appeals and Interferences (the Board), rejecting claims 2 through 25 and 27 through 31, all the claims at issue of Spada and Wilczynski (hereinafter Spada) patent application Serial No. 859,057, filed May 2, 1986 and entitled "Pressure Sensitive Adhesives and Manufactured Articles", is affirmed.

The Invention

The Spada invention is a pressure sensitive [**2] adhesive composition comprising a water-based latex containing a normally tacky copolymer made from specified classes and proportions of monomers and having a glass transition temperature (T[g]) [1] of 0 degreesC or less. Claim 31 was treated by the parties as representative:

Claim 31. A pressure sensitive adhesive composition comprising a water-base latex comprising a continuous aqueous medium containing dispersed particles of a normally tacky polymer having a T[g] of about 0 degreesC. or less and comprising at least about 60 weight percent olefinically unsaturated carboxylic acid ester monomers and at least about 0.1 weight percent of at least one polymerizable functional monomer of the formula:

R[5] O

R[6] - CH = C - R[1] - C - CH[2] - X

in which R[1] is a divalent organic radical of at least 3 atoms in length, R[5] and R[6] are independently selected from hydrogen, hydroxy, halo, thio, amino or monovalent organic radicals, and X is -CO-R[4] or -CN wherein R[4] is hydrogen or a monovalent organic radical.

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1 Glass transition temperature (T[g]) is defined as the temperature (or temperature range) at which an amorphous polymer changes from a hard, rigid, glassy state to a soft, flexible, rubbery state. S. Rosen, Fundamental Principles of Polymeric Materials § 8.1 (1982).

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[**3] The Spada disclosure broadly is coextensive with claim 31. While claim 31 requires that the polymers comprise members of two general classes of monomers, Spada's specific examples illustrate polymers in which members of three general classes of monomers are present.

The first class of monomer required by Spada is an olefinically unsaturated carboxylic acid ester that is present in at least about 60 weight percent of the polymer. Representative examples show 96.5 weight percent butyl acrylate (Example 2), and a combination of 48 weight percent butyl acrylate and 48 weight percent 2-ethylhexyl acrylate (Example 11).

Spada's second required class of monomer is a "polymerizable functional monomer" present in "at least about 0.1 weight percent" of the polymer (claim 31). The illustrative examples show 1-2 weight percent acetoacetoxyethyl methacrylate (AAEMA).

Spada's specification states that preferred polymer compositions include at least about 0.1 weight percent of a third [*707] class of monomer, an olefinically unsaturated carboxylic acid. Examples are 1.5 weight percent methacrylic acid (Example 2) and 3 weight percent acrylic acid (Example 7).

All of Spada's claims [**4] require that the T[g] of the claimed tacky polymers is about 0 degreesC or less, and that the products are pressure-sensitive adhesives.

The claims were rejected as unpatentable in view of the Smith reference, United States Patent No. 3,554,987, issued January 12, 1971. The Spada disclosure and the Smith reference both show polymers of the same monomers, in overlapping ratios of components. However, the products that Smith and Spada obtain are described as quite different.

The Smith Reference

Smith describes water-based latexes containing dispersed particles of polymers made from certain classes and proportions of monomers. The polymers are used in binding agents in photographic gels and films.

In most of Smith's examples three monomers are present, as in Spada's examples. The first monomer in Smith's preferred polymers is an olefinically unsaturated carboxylic acid

ester, in at least 50 percent by weight of polymer. In Smith's examples this component is illustrated, inter alia, as 75.7 molar percent butyl acrylate (Example 5), and 72.4 weight percent ethyl acrylate (Example 15).

Smith's second monomer used in preparing his preferred polymers is a polymerizable functional [**5] monomer like that described by Spada, present in about 2-20 weight percent of the polymer. Smith's examples include polymers containing 9.4 molar percent of acetoacetoxyethyl acrylate (AAEA) (Example 5), and 3.5 weight percent AAEMA (Example 15). Spada incorporated by reference the entire disclosure of the Smith patent, as showing polymerizable functional monomers suitable and preferred for use in the Spada polymers, and the preparation of these monomers.

The preferred polymers of Smith contain a third monomer, as do Spada's, and most of Smith's examples include acrylic acid. Thus, in Smith's Example 5 the complete polymer composition is 75.7 molar percent butyl acrylate, 9.4 molar percent AAEA, and 14.9 molar percent acrylic acid. In Smith's Example 15 the composition is 72.4 weight percent ethyl acrylate, 3.5 weight percent AAEMA, and 24.1 weight percent acrylic acid.

Smith states that emulsions containing his polymers have improved properties of hardness, resistance to abrasion, good adhesion, and dimensional stability. Smith does not show or suggest that his polymer latexes can form a normally tacky pressure-sensitive adhesive -- properties admitted to be different from hardness [**6] and abrasion resistance.

Discussion

The Board affirmed the rejection of Spada's claims under 35 U.S.C. §§ 102, 103, HN1 this hybrid rejection having apparently been made on the theory that if the claimed subject matter was novel, i.e. not anticipated, in terms of section 102, then it would have been obvious under section 103. [2] The Commissioner on this appeal concentrates on the rejection for anticipation. The Commissioner argues that a prima facie case [3] of anticipation is made by the Smith disclosure of polymers that are apparently identical [*708] to those of Spada, although the properties described by Smith are different from those that are reported by Spada and included as express limitations in Spada's claims.

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2 The court has accepted HN2 the PTO's practice of basing rejections on sections 102 or 103 in the alternative, provided that the appellant was fully apprised of all the grounds of rejection. See, e.g., In re Pearson, 494 F.2d 1399, 1402 & nn. 2-3, 181 USPQ 641, 644 & nn. 2-3 (CCPA 1974). [**7] 3 HN3 The prima facie case is a procedural tool which, as used in patent examination (as by courts in general), means not only that the evidence of the prior art would reasonably allow the conclusion the examiner seeks, but also that the prior art compels such a conclusion if the applicant produces no evidence or argument to rebut it. See Black's Law Dictionary 1071 (5th Ed. 1979). See generally In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984) (citing cases showing the

evolution of the concept in patent examination of prima facie obviousness as a legal inference drawn from uncontradicted evidence). Upon rebuttal, the decision is made on the entirety of the record. Id.

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HN4 Rejection for anticipation or lack of novelty requires, as the first step in the inquiry, that all the elements of the claimed invention be described in a single reference. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 [**8] (Fed. Cir.), cert. denied, 493 U.S. 853, 110 S. Ct. 154, 107 L. Ed. 2d 112 (1989). Further, the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it. Akzo N.V. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1479, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909, 96 L. Ed. 2d 382, 107 S. Ct. 2490 (1987); In re Coker, 59 C.C.P.A. 1185, 463 F.2d 1344, 1348, 175 USPQ 26, 29 (CCPA 1972).

Spada argues that Smith does not describe Spada's claimed invention, for to find anticipation "all limitations in the claims must be found in the reference since the claims measure the invention." In re Lange, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Spada states that since his compositions are claimed as pressure-sensitive adhesives containing a tacky polymer having a T[g] below 0 degreesC, they can not be anticipated. Spada argues that since the Smith products are hard, abrasion-resistent solids, they are ipso facto different.

[**9] HN5 The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition. [4] Titanium Metals Corp. v. Banner, 778 F.2d 775, 780, 782, 227 USPQ 773, 777-78, 778 (Fed. Cir. 1985); In re Pearson, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974); In re Lemin, 51 C.C.P.A. 942, 326 F.2d 437, 440, 140 USPQ 273, 276 (CCPA 1964). Thus, the initial inquiry is to the novelty of the composition. Titanium Metals, 778 F.2d at 780, 227 USPQ at 777.

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4 All of Spada's claims are composition claims. The issue is not before us of whether Spada may have discovered a new use of a known composition, which use may be patentable as a process. 35 U.S.C. § 101. See In re Hack, 44 C.C.P.A. 954, 245 F.2d 246, 248, 114 USPQ 161, 163 (1957).

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[**10] The Board held that the compositions claimed by Spada "appear to be identical" to those described by Smith. While Spada criticizes the usage of the word "appear", we think that it was reasonable for the PTO to infer that the polymerization by both Smith and Spada of identical monomers, employing the same or similar polymerization techniques, would produce polymers having the identical composition. HN6 Products of

identical chemical composition can not have mutually exclusive properties. See In re Papesch, 50 C.C.P.A. 1084, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) (a chemical compound and its properties are inseparable).

While the art and science of polymer chemistry may be distinguished from that of simpler compounds and compositions, in Spada's case we conclude that the Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty. See, e.g., In re Thorpe, 777 F.2d 695, 697-98, 227 USPQ 964, 966 (Fed. Cir. 1985), wherein the examiner's [**11] rejection of product-by-process claims under §§ 102, 103, based on similarity of reactants, reaction conditions, and properties, amounted to a prima facie case of unpatentability.

HN7 In response to the PTO's asserted prima facie case the applicant may argue that the inference of lack of novelty was not properly drawn, for example if the PTO did not correctly apply or understand the subject matter of the reference, or if the PTO drew unwarranted conclusions therefrom. However, when the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. In re King, 801 F.2d 1324, 1327, 231 USPQ 136, 138 (Fed. Cir. 1986); In re Ludtke, 58 C.C.P.A. 1159, 441 F.2d 660, 664, 169 USPQ 563, 566 (CCPA 1971). Spada offered no such showing.

[*709] The Board suggested that Spada provide some scientific explanation for the asserted differences between the properties of his compositions and those described by Smith. While [**12] HN8 an inventor is not required to understand how or why an invention works, we think that the PTO was correct, in view of the apparent identity of the compositions, in requiring Spada to distinguish [5] his compositions from those of Smith. Although HN9 newly discovered properties can be the basis of claims to novel polymers, E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co., 849 F.2d 1430, 1435, 7 USPQ2d 1129, 1133 (Fed. Cir.), cert. denied, 488 U.S. 986, 109 S. Ct. 542, 102 L. Ed. 2d 572 (1988), Spada did not overcome, with argument or evidence, the apparent chemical identity of his polymers and those of Smith. Spada showed no error, in science or in law, in the Board's holding that the products appeared to be the same and thus that Spada's products were not new.

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5 It was discussed at oral argument that the Spada invention may not be "particularly point[ed] out and distinctly claim[ed]", in the words of 35 U.S.C. § 112, paragraph 2. No rejection had been made under section 112. The Solicitor stated that such a rejection was inappropriate because the claims were "not vague". But see Burlington Indus. v. Quigg, 822 F.2d 1581, 1583-84, 3 USPQ2d 1436, 1438 (Fed. Cir. 1987) (whether claims were too broadly written is not a section 103 determination but an issue of claim imprecision under section 112). See also In re Muchmore, 58 C.C.P.A. 719, 433 F.2d 824, 824-25, 167 USPQ 681, 682 (CCPA 1970) ("there is sometimes a close relationship between indefiniteness under § 112, second paragraph, and obviousness under § 103").

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[**13] Spada pointed to his data wherein polymers containing varying amounts of AAEMA showed greatly increased shear strength without significant loss in tack, compared with polymers without the AAEMA. We agree with Spada that this result is not suggested in the Smith reference. However, these data did not relate to the fundamental question of the novelty of Spada's compositions in view of those of Smith. HN10 Without novelty, evidence of unobviousness is superfluous.

As we observed supra, HN11 discovery of an unobvious property and use does not overcome the statutory restraint of section 102 when the claimed composition is known. While Spada's position is that his polymers are not anticipated by the polymers of Smith because their properties are different, Spada was reasonably required to show that his polymer compositions are different from those described by Smith. This burden was not met by simply including the assertedly different properties in the claims. [**14] HN12 When the claimed compositions are not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.

The Board's decision rejecting all of the claims is

AFFIRMED

IN RE RONALD D. SCHOENWALD and CHARLES F. BARFKNECHT

91-1421

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

964 F.2d 1122; 1992 U.S. App. LEXIS 10181; 22 U.S.P.Q.2D (BNA) 1671

May 12, 1992, Decided

PRIOR HISTORY: [**1] Appealed from: U.S. Patent and Trademark Office Board of Patent Appeals and Interferences

DISPOSITION: AFFIRMED

CASE SUMMARY

PROCEDURAL POSTURE: Appellant applicants sought review of a judgment from the United States Patent and Trademark Office Board of Patent Appeals and Interferences, which affirmed the patent examiner's rejection of claims in their patent application for anticipation under 35 U.S.C.S. § 102(b) by a printed publication.

OVERVIEW: Appellant applicants had submitted their patent for examination. The patent examiner rejected claims in their application for anticipation by a printed publication more than one year prior to the critical filing date in violation of 35 U.S.C.S. § 102(b). The Board of Patent Appeals and Interferences affirmed the claim rejection and appellants sought review. On appeal, the court found that a reference to a patented invention was not required to disclose the invention's utility in order for it to be anticipatory for purposes of 35 U.S.C.S. § 102(b). The court affirmed, finding that the compound that appellants were attempting to patent was not new and that they were entitled only to a method patent on the new use they had discovered for the old compound.

OUTCOME: The court affirmed the judgment, which upheld the rejection of appellant applicants' patent claims for being anticipatory.

CORE TERMS: patent, compound, prior art, composition, invention, dry, bulb, tear, anticipatory, disclosure, anticipate, disclose, polymer, syndrome, printed publication, patentability, anticipated, discovery, patented, Patent Act, fully disclosed, anticipation, unobvious, dictum, artificial

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Patent Law > Anticipation & Novelty > General Overview

HN1 Paramount among the patentability requirements is that that which is sought to be patented must be new.

Patent Law > Anticipation & Novelty > Description in Patents
Patent Law > Anticipation & Novelty > Description in Publications
Patent Law > Statutory Bars > General Overview

HN2 Under 35 U.S.C.S. § 102(b), one is not entitled to a patent on a compound if it was patented or described in a printed publication in this or a foreign country more than one year prior to the date of the application for patent in the United States.

Patent Law > Anticipation & Novelty > General Overview

HN3 While the mere naming of a compound may not be enough for anticipation under 35 U.S.C.S. § 102(b), a reference which describes and enables has been held sufficient.

Patent Law > Ownership > Patents as Property
Patent Law > Subject Matter > Processes > New Uses
Patent Law > Subject Matter > Products > Compositions of Matter

HN4 Where there has been use of an article or where the method of its manufacture is known, more than a new advantage of the product must be discovered in order to claim invention. It is contrary to the letter of the patent laws that patents should be granted for old compositions of matter based upon new uses.

Patent Law > Anticipation & Novelty > General Overview
Patent Law > Utility Requirement > Proof of Utility

HN5 Utility need not be disclosed to anticipate a claim to a compound under 35 U.S.C.S. § 102(b) but must be for enablement under 35 U.S.C.S. § 112.

Patent Law > Anticipation & Novelty > General Overview
Patent Law > Inequitable Conduct > General Overview

HN6 When the claimed compositions are not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.

COUNSEL: Edmund J. Sease, Zarley, McKee, Thomte, Voorhees & Sease, of Des Moines, Iowa, argued for appellant.

Fred E. McKelvey, Solicitor, Office of the Solicitor, of Arlington, Virginia, argued for appellee. With him on the brief were Richard E. Schafer, Associate Solicitor and Joseph G. Piccolo, Assistant Solicitor.

JUDGES: Before NEWMAN, ARCHER, and MAYER, Circuit Judges.

OPINION BY: MAYER

OPINION

[*1122] MAYER, Circuit Judge.

Ronald D. Schoenwald and Charles F. Barfknecht appeal from a decision of the Patent and Trademark Office Board of Patent Appeals and Interferences which affirmed the rejection of Claim 9 of Patent Application No. 257,826 for anticipation. Appeal No. 89-3349 (Dec. 17, 1990). We affirm.

Background

The application was filed on October 14, 1988, and claimed compounds which are used in ophthalmic compositions to treat dry eye syndrome. Claim 9, the only remaining claim, is to the most preferred compound, N-cyclohexyl-N-methyl-2-phenylethylamine, and its biologically acceptable salt forms.

As its name implies, dry eye syndrome is caused by a disruption in normal tear production, resulting in "dry eyes." [**2] Previously, dry eye syndrome could only be treated by lubricating the eyes with artificial tear substitutes. This treatment was unsatisfactory because artificial tears dry quickly, and a sufferer of dry eye syndrome would have to apply the lubricant continually, as often as once an hour. In contrast, Schoenwald began using the compound set out in Claim 9, among others, as "tear stimulants" which, when applied topically to the eye, stimulate the lacrimal glands so they produce natural tears, eliminating the need for repeated reapplication. This method of treatment was claimed in the parent of the present application which resulted, on April 11, 1989, in U.S. Patent 4,820,737.

The Patent and Trademark Office Board of Patent Appeals and Interferences affirmed the examiner's rejection of Claim 9 as anticipated under 35 U.S.C. § 102(b) (1988) by a printed publication, Bumgardner et al., J. Org. Chem., Vol. 44, No. 14, "Reactions of Alkylbenzyldimethylammonium Halides with Amide in Liquid Ammonia," pages 2348-54 (1979) (Bumgardner). Schoenwald does not dispute that the compound of Claim 9 is adequately described and enabled by Table 1, Scheme III and age 2353 of Bumgardner.

Nor does [**3] he dispute that Bumgardner does not disclose [*1123] a utility for the compound. His argument is that a reference must disclose a utility before it can be an anticipatory reference under section 102(b). Relying on In re Hafner, 56 C.C.P.A. 1424, 410 F.2d 1403, 161 USPQ 789 (CCPA 1969), and its progeny, the board held that it need not.

Discussion

HN1 Paramount among the patentability requirements is that that which is sought to be patented must be new. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 780, 227 USPQ 773, 777 (Fed. Cir. 1985). Simply put, the compound claimed by Schoenwald is not new. HN2 Under section 102(b), one is not entitled to a patent on a compound if it "was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." Phrased differently, section 102(b) prohibits the patenting of a compound if it is anticipated by a prior printed publication. HN3 While the mere naming of a compound may not be enough for anticipation, a reference which describes and enables has been held sufficient. In re Wiggins, 488 F.2d 538, 543, 179 USPQ 421, 425 (CCPA 1973), [**4] In re Brown, 51 C.C.P.A. 1254, 329 F.2d 1006, 1011, 141 USPQ 245, 249 (CCPA 1964). But Schoenwald would go further: he argues that an anticipatory reference must also disclose a use.

Even before the 1952 Patent Act, the Supreme Court stated, "If A without mentioning the element of strength patented a bulb which was extra strong, B could not obtain a patent on the bulb because of its strength, though he was the first to recognize that feature of it." General Elec. Co. v. Jewel Incandescent Lamp Co., 326 U.S. 242, 247, 90 L. Ed. 43, 66 S. Ct. 81 (1945). Accordingly, the Court invalidated a patent for a frosted light bulb because the prior art disclosed the bulb's design, even though the prior art did not disclose the property of the bulb that made it useful, its strength.

[The patentee] found latent qualities in an old discovery and adapted it to a useful end. But that did not advance the frontiers of science in this narrow field so as to satisfy the exacting standards of our patent system. HN4 Where there has been use of an article or where the method of its manufacture is known, more than a new advantage of the product must be discovered in order to claim invention.

Id. at 248. [**5] See also In re Thuau, 30 C.C.P.A. 979, 135 F.2d 344, 346, 57 USPQ 324, 325 (CCPA 1943) (it is "contrary to the letter of the patent laws that patents should be granted for old compositions of matter based upon new uses").

The first case to address the issue under the 1952 Patent Act was In re Hafner, 56 C.C.P.A. 1424, 410 F.2d 1403, 161 USPQ 783. Appellants argue that we should ignore Hafner because the pertinent language is dictum, Hafner is a section 112 case, or it is simply incorrect. In that case, applicant attempted to claim the priority date of his two prior German patent applications. But, subsequent to the German filing date, an article by one Arnold discussing the alleged invention and one of Hafner's German patent

applications were published. Because neither publication taught the public "how to use" the invention, the court held that they were not "enabling" under section 112. Therefore, the applicant was not entitled to the priority date of the German applications. However, the court held the Hafner and Arnold publications were anticipatory references under section 102. Applicant remonstrated that the Patent Office's policy of requiring [**6] disclosure of utility to obtain a patent, but not to anticipate an application, is "inconsistent and unfair." Appellants here argue likewise: "What constitutes the measure of 'the invention' to determine whether what is claimed is a legally recognizable invention must also constitute 'the invention' for determining whether something lacks novelty under 35 U.S.C. 102(b)." The Hafner court responded,

In essence, appellant is contending that a double standard should not be applied in determining the adequacy of a disclosure to anticipate under § 102, on the one hand, and to support the patentability of a claim under § 112 on the other. He [*1124] feels that a disclosure adequate for the one purpose is necessarily adequate for the other but, unhappily for him, this is not so. As we shall develop, a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim.

[**7]

Id. at 1405, 161 USPQ at 785 (footnotes omitted). This discussion was not dictum because by adhering to the rule that HN5 ↑utility need not be disclosed to anticipate a claim to a compound, but must be for enablement, the rejection of applicant's claims was affirmed. To the same effect were In re Samour, 571 F.2d 559, 563, 197 USPQ 1, 5 (CCPA 1978) ("Appellant's further argument that 'some practical utility' for [the invention] must be disclosed in the prior art before [the prior art reference] can serve as a statutory bar . . . . it also not persuasive"), and In re Donohue, 632 F.2d 123, 126 n.6, 207 USPQ 196, 199 n.6 (CCPA 1980) ("proof of utility is not a prerequisite to availability of a prior art reference under 35 U.S.C. § 102(b)").

Only recently, this court reiterated, "The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, can not impart patentability to claims to the known composition." In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990). The facts [**8] there were similar to this case in that the board found that Spada's polymer composition appeared to be identical to the prior art. As we discussed, id. at 709, 15 USPQ2d at 1658:

discovery of an unobvious property and use does not overcome the statutory restraint of section 102 when the claimed composition is known. While Spada's position is that his polymers are not anticipated by the polymers of Smith because their properties are different, Spada was reasonably required to show that his polymer compositions are different from those described by Smith. This burden was not met by simply including the assertedly different properties in the claims. HN6 ↑When the claimed compositions are

not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.

So it is beyond argument that no utility need be disclosed for a reference to be anticipatory of a claim to an old compound. The compound appellants are attempting to patent is not new -- the use they discovered is, and they received a method patent for that. Their complaint that this is insufficient because their reward should be [**9] consistent with the full extent of their contribution is hollow. Their contribution was finding a use for the compound, not discovering the compound itself. Therefore they are being rewarded fully for their contribution; any more would be a gratuity.

Conclusion

Accordingly, the decision of the board is affirmed.

AFFIRMED

IN THE MATTER OF THE APPLICATION OF LESLIE FREDERICK WIGGINS, JOHN WILLIAM JAMES and MAURICE WARD GITTOS.

Patent Appeal No. 8806

UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

488 F.2d 538; 1973 CCPA LEXIS 254; 179 U.S.P.Q. (BNA) 421

October 11, 1973

PRIOR HISTORY: [**1] Serial No. 526,707.

CASE SUMMARY

PROCEDURAL POSTURE: Appellants sought review of a decision of the patent office Board of Appeals sustaining the patent examiner's rejection of claims of appellants' application directed to compounds useful for treating Parkinson's disease. All of the claims were rejected under 35 U.S.C.S. § 102 (b), and some of the claims were further rejected under 35 U.S.C.S. § 112.

OVERVIEW: Appellants' patent application directed to compounds useful for treating Parkinson's disease was rejected, under 35 U.S.C.S. §§ 102 (b) and 112, because appellants were claiming an invention that was broader than any described in their specification and were not distinctly claiming that which they regarded as their invention. The court noted that words in patent claims were to be given their broadest reasonable interpretation consistent with the specification, where the patent had not yet issued and the applicant had an opportunity to change them. Nevertheless, the court found that the language used by appellants in their claims could have been interpreted to include other compound members than those noted by appellants. Further, the court held that the rejection of appellants' claims under 35 U.S.C.S. § 102 (b), based upon a previously published article, was improper since the article itself did not disclose all that was necessary to put the compounds in the hands of the public. The court continued that the compounds listed in the article constituted nothing more than speculation, and therefore did not mandate a rejection of appellants' claims.

OUTCOME: Decision rejecting appellants' patent claims was modified where the claim language used by appellants could have been interpreted to include other compound members than those noted by appellants, but the compounds named in a previously published article and within the scope of the claims in issue were not described in a printed publication, as meant by the relevant

portion of applicable statute.

CORE TERMS: compound, atom, heterocyclic, acid, ring, examiner's, oxygen, nitrogen, carbon, invention, illustration, patent, consisting, alkyl, rejection of claims, thiobarbituric, oxobarbituric, specification, straight-chain, unsubstituted, condensation, malonic, chain, ester, temperature, enabling, prepare, naming, skill, methyl-substituted

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Patent Law > Claims & Specifications > Description Requirement > General Overview
Patent Law > Jurisdiction & Review > Subject Matter Jurisdiction > Appeals
Patent Law > U.S. Patent & Trademark Office Proceedings > Reissues > General Overview

HN1 Words in patent claims are to be given their broadest reasonable interpretation consistent with the specification where the patent has not yet issued and the applicant has an opportunity to change them.

OPINION BY: ALMOND

OPINION

[*538] ALMOND, Senior Judge.

This is an appeal from the decision of the Patent Office Board of Appeals sustaining the examiner's rejection of claims 1, 2 and 10 of appellants' application [1] directed to compounds useful [*539] for treating Parkinson's disease. All these claims were rejected under 35 USC 102(b) and claims 1 and 10 were rejected under 35 USC 112. We reverse in part and affirm in part.

- - - - - - - - - - - - - - Footnotes - - - - - - - - - - - - - -
1 Serial No. 526,707 filed February 11, 1966.

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Invention

Appellants' invention is most broadly set forth in claim 1 reproduced below:

1. A compound having anti-Parkinsonism activity selected from the class consisting of compounds of the formula:

[Graphic omitted. See illustration in original.]

and pharmaceutically acceptable salts thereof, in which formula X is selected from the group consisting of oxygen and sulphur, R(1) is selected from the group consisting of:

(A) [Graphic omitted. See illustration in original.] wherein R(3) represents lower alkyl,

R(4) represents lower alkyl and A represents a group selected from the class consisting of unsubstituted and methyl-substituted straight-chain alkylene of [**2] two to three chain carbon atoms;

(B) [Graphic omitted. See illustration in original.] wherein [Graphic omitted. See illustration in original.] represents a saturated heterocyclic group of five to seven ring atoms, from one to two nitrogen atoms, and up to one oxygen atom, and A represents a group selected from the class consisting of unsubstituted and methyl-substituted straight-chain alkylene of two to three chain carbon atoms; and

(C) R(5) - (CH(2))(n) -, wherein n is a positive whole number up to 2 and R(5) is a saturated heterocyclic group of five to seven ring atoms, up to one oxygen atom and from one to two nitrogen atoms, said heterocyclic group containing a member selected from the group consisting of unsubstituted and lower-alkyl-substituted basic ring nitrogen atoms spaced away from the adjacent carbonyl groups in the barbituric acid ring by from three to five carbon atoms;

and R(2) is selected, when X is oxygen, from the group consisting of:

(D) phenyl, halogenophenyl, hydroxyphenyl, lower alkylphenyl and lower alkoxyphenyl;

and when X is sulphur, from the group consisting of:

(E) phenyl, halogenophenyl, hydroxyphenyl, lower alkylphenyl, lower alkoxyphenyl, [**3] cyclohexyl, benzyl and straight-chain and branched chain alkyls having from three to seven carbon atoms.

Dependent claim 2 is somewhat narrower in scope than claim 1 in its definition of R(1) and R(2). Claim 10 is directed to the "acid addition salt form" of the compound of claim 1.

When X is oxygen, the compounds embraced by claim 1 are referred to as "oxobarbituric acids." Similarly, when X is sulfur, the compounds are referred to as "thiobarbituric acids." According to appellants' specification, these compounds are useful for the treatment of Parkinson's disease (paralysis agitans), a disease of the nervous system sometimes referred to as "shaking palsy."

The compounds encompassed by the claims can, for the most part, be prepared by a process well known to the prior art involving the condensation of urea or thiourea with a disubstituted malonic ester in the presence of a refluxing solution of sodium in an alcohol [*540] (a sodium alcoholate). The disubstituted malonic ester has the formula:

[Graphic omitted. See illustration in original.]

wherein R is a lower alkyl group, preferably ethyl. Appellants term this process a "high temperature condensation."

[**4] Appellants found that certain oxo- and thiobarbituric acids could not be prepared this way because the malonic ester required for the synthesis was unstable and decomposed in the refluxing solvent. The malonic esters susceptible to this decomposition are described by appellants as those having the formula:

[Graphic omitted. See illustration in original.]

wherein R(1) represents:

(A) [Graphic omitted. See illustration in original.] wherein R(3) represents a lower alkyl group and A represents an unsubstituted or methyl-substituted straight-chain alkylene radical having 2 or 3 chain carbon atoms; or

(B) [Graphic omitted. See illustration in original.] wherein [Graphic omitted. See illustration in original.] represents a heterocyclic group containing from five to seven ring atoms and A represents an unsubstituted or methyl-substituted straight-chain alkylene radical having 2 or 3 chain carbon atoms; or

(C) R(5) - (CH(2))(n) -, wherein n is 1 or 2 and R(5) represents 2-pyridyl or N-methyl-2-piperidinyl; and

Z represents hydrogen or at least one halogen, lower alkyl or lower alkoxy substituent, provided that when R represents a dimethylaminoalkyl group which is [**5] not substituted by methyl in the alpha position of the alkyl group, Z cannot represent hydrogen, but must be at least one halogen, lower alkyl or lower alkoxy substituent.

Appellants discovered that decomposition of the malonic ester could be avoided by carrying out the condensation at or below 30 degrees C. However, at this temperature only the thiobarbituric acids could be obtained since urea, unlike thiourea, would not undergo condensation. Therefore, in order to obtain oxobarbituric acids which could not be prepared by the prior art process, appellants added yet another refinement to their process. First, they prepared the thiobarbituric acid analogue of the desired oxobarbituric acid which was then oxidized by a known process to the corresponding oxobarbituric acid. Appellants refer to this process as a "low temperature condensation."

Opinion

Rejection Under § 112

In support of the rejection of claims 1 and 10 under § 112, the examiner, in his "Supplemental Examiner's Answer On Remand," made the following observations:

The definitions of [Graphic omitted. See illustration in original.] and "R(5)" are indefinite and too broad. The definitions particularly point [**6] out the nature of only one, two, or three, of the five to seven ring atoms. The claims are indefinite as to what other ring atoms can be present. The claims are also indefinite as to what and how [*541] many substituents the heterocyclic groups can have, if any. The claims are too broad in that there is no proper support for such rings as pyrazolidinyl, isoxazolidinyl, oxadiazolidinyl, etc.-i.e. rings wherein the heteroatoms are not separated by carbon atoms.

* * *

Re the rejection as failing to properly define the invention, appellants argue first that "a saturated heterocyclic group of ... from one to two nitrogen atoms, and up to one oxygen atom" means "a saturated heterocyclic group in which the heteroatoms are all selected from the group consisting of from one to two nitrogen atoms and up to one oxygen atom". Concededly, this is a possible construction of the language, but the language is open to other interpretations. * * * Support for appellants' construction may be found in the fact that the specification discloses only heterocyclic groups containing nitrogen or nitrogen and oxygen.

It would appear that the examiner was of the opinion that appellants were [**7] claiming an invention that was broader than any described in their specification (a 1st paragraph, § 112 rejection) and were not distinctly claiming that which they regarded as their invention (a 2nd paragraph, § 112 rejection). The board agreed with the examiner's rejection, commenting, in part, as follows:

Appellants' arguments do not persuade us of error in the Examiner's rejection. The terminology employed is so loose as to be indefinite and to be entirely speculative as to the inclusion of groups forming final products having the therapeutic activity herein required. * * *

* * *

It must also be noted that the claim terminology is so broad that it does not even require that the heterocyclic group contain a carbon atom. Heterocyclic ring systems containing phosphorus, boron, silicon, and other elements in addition to nitrogen and oxygen without the inclusion of carbon atoms are well-known and could not be expected to produce compounds having the properties herein claimed.

In our view, the rejection under § 112 was properly made, at least insofar as it was based on the 2nd paragraph of § 112. That paragraph requires the applicant to "particularly point out and distinctly [**8] claim the subject matter sought to be patented." In re Borkowski, 57 CCPA 946, 921, 422 F.2d 904, 909, 164 USPQ 642, 645 (1970). If the scope of the invention sought to be patented is unclear from the language of the claim, a second paragraph rejection will properly lie.

In the instant case, the Patent Office questions whether the term "heterocyclic group" as defined in the claims possesses the requisite definiteness. Both the examiner and the board felt the term was not precise enough to allow the scope of the claims involved to be accurately determined. Appellants seek to overcome their specific criticisms by arguing that:

* * * the claims clearly define the maximum breadth, namely, heterocyclic rings containing carbon and nitrogen, or carbon, nitrogen, and oxygen, having from five to seven ring atoms, one or two nitrogen atoms, and up to one oxygen atom. This is a rather limited scope, as heterocyclic rings go. There are many more heterocyclic compounds excluded by the claims than are included by them, such as, for instance, heterocyclic rings containing the two or more oxygen atoms, three or more nitrogen atoms, or one or more sulfur atoms, as well as other types of hetero [**9] atoms.

However, we agree with the examiner that appellants' interpretation of the scope of the claim is but one possible construction and that other, broader constructions are possible that are not unreasonable in light of the words of the claims. HN1 Words in claims are to be given "their broadest reasonable interpretation consistent with the specification where [*542] the patent has not yet issued and the applicant has an opportunity to change them." In re Finsterwalder, 58 CCPA 871, 876, 436 F.2d 1028, 1032, 168 USPQ 530, 534 (1971).

Applying this standard to claims 1 and 10, it is our view that the board was correct when it concluded that the "heterocyclic group" in those claims could be interpreted to include other members than those noted by appellants. Furthermore, the examiner, in his answer, indicated that appellants had support in the specification for a claim of the same scope that appellants would now have us give claims 1 and 10. Therefore, we do not think it would have been difficult to employ language in the claims precisely limiting them to that scope.

In view of our affirmance of the rejection under § 112 on the ground that the claims do not satisfy the [**10] requirements of the 2nd paragraph, it is not necessary for us to consider whether a rejection made under the 1st paragraph would have been justified.

Rejection Under Section 102(b)

The rejection of claims 1, 2 and 10 under section 102(b) was based upon an article [2] published by Giudicelli et al. (Giudicelli). This reference reports the syntheses of a number of oxobarbituric acid derivatives (X=oxygen) and studies of their effect as sedatives. None of the compounds actually prepared and studied fall within the scope of the claims involved here. However, Giudicelli mentions by name two compounds that do, phenyl-beta-piperidinoethyl barbituric acid and phenyl-beta-morpholinoethyl barbituric acid, whose syntheses were unsuccessfully attempted. The examiner recognized that the failure of Giudicelli to make these compounds was a defect in the reference. Therefore, he cited a second reference, a patent to Donnison, [3] which discloses a process for making

oxo- and thiobarbituric acids. This process is similar to appellants' low temperature process.

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2 Annales Pharm. Francaises, Vol. 15, 1957, pp. 533-546. 3 U.S. 2,876,225 issued March 3, 1959.

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The examiner concluded [**11] that Donnison's process could be used to prepare the compounds named by Giudicelli. The significance of this conclusion can be seen from the legal analysis of that situation, stated by him as follows:

Giudicelli et al. could not prepare these compounds by their chosen method. However, the test of an "enabling disclosure" is not whether the reference teaches how to make the compounds, but whether the reference taken with the remainder of "the prior art is such as to place the disclosed 'compound' in the possession of the public."

The examiner's authority for this test was the decision of this court in In re Brown, 51 CCPA 1254, 329 F.2d 1006, 141 USPQ 245 (1964). See also In re LeGrice, 49 CCPA 1124, 301 F.2d 929, 133 USPQ 365 (1962); In re Sheppard, 52 CCPA 859, 339 F.2d 238, 144 USPQ 42 (1964); In re Hoeksema, 55 CCPA 1493, 399 F.2d 269, 158 USPQ 596 (1968); In re Collins, 59 CCPA 1170, 462 F.2d 538, 174 USPQ 333 (1972). In his view, Giudicelli is an "enabling disclosure" since Donnison's process could be used to make the named compounds, thereby putting them in the possession of the public. The board agreed.

The examiner's rationale necessarily presumes that Giudicelli [**12] both describes the invention and would enable one skilled in the art to make the invention, the former by merely naming the compounds and the latter by viewing Donnison as evidence that one skilled in the art could make the named compounds, thereby making them available to the public.

Appellants argue that the rejection is improper since Giudicelli by itself does not disclose all that is necessary to put the compounds in the hands of the public. Because the Patent Office had to rely upon Donnison to overcome this defect in Giudicelli, appellants insist that the rejection must be considered as having been made over a combination of references. In their view, a rejection [*543] based upon a combination of references is proper only if the statutory basis is 35 USC 103. Alternatively, appellants argue that the process taught by Donnison could not be used to make the named compounds.

The solicitor states the issue as to whether § 102(b) can be the proper statutory basis as follows:

Does the rejection of compound claims for anticipation under 35 U.S.C. 102(b) preclude reliance on additional evidence to show that one of ordinary skill in the art would have known how to prepare [**13] the claimed compounds at the time appellants' alleged invention was made?

The answer to the solicitor's question, and certainly the one desired by him, must be "No." Every patent application and reference relies to some extent upon knowledge of persons skilled in the art to complement that disclosed in order that it be "enabling" within the meaning of § 112 and to satisfy the requirements of a reference under § 102. For example, a reference describing an oil refinery need not describe how to make bolts and rivets in order to be considered "enabling." The hypothetical just stated is an extreme case. In closer cases, where it might be reasonably doubted that a reference or patent application satisfies § 102 or § 112, other references can be cited as evidence of the level of skill in the art.

However, we do not think that the outcome of this case revolves about the answer to the above-stated question. The defect in the issue, as stated by the solicitor, is that it presumes that the naming of the compounds by Giudicelli constitutes a description of the invention within the meaning of § 102(b). We do not accept this presumption. In our view, Giudicelli's listing of the compounds [**14] by name constituted nothing more than speculation about their potential or theoretical existence. The mere naming of a compound in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed [4] until a date later than that of the reference.

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4 We do not mean to suggest that we have actually evaluated the process taught by Donnison and concluded that it could be used to prepare the claimed compounds. As this is irrelevant to our decision, we express no opinion on this point.

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If we were to hold otherwise, lists of thousands of theoretically possible compounds could be generated and published which, assuming it would be within the level of skill in the art to make them, would bar a patent to the actual discoverer of a named compound no matter how beneficial to mankind it might be. In view of the fact that the purpose sought to be effectuated by the patent law is the encouragement of innovation, such a result would be repugnant to the statute. Therefore, we hold that the compounds named in Giudicelli and within the scope of the claims [**15] in issue were not "described in a printed publication" as meant by the applicable portion of § 102(b). This dictates a reversal of the rejection of claims 1, 2 and 10 under that section.

Our holding does not mean that a reference merely naming a compound is without effect at all. It may be used as evidence of obviousness under § 103 for all it fairly suggests to one of ordinary skill in the art. In fact, the solicitor suggests in his brief that it wouldn't

matter in this case whether we view the statutory basis of the rejection as § 102(b) or § 103. We cannot agree.

In evaluating whether a rejection made under § 103 is proper, evidence not pertinent to a rejection made under § 102(b) may have relevance, i.e., commercial success, unexpected results, etc. For example, evidence of commercial success no matter how striking could not overcome a rejection of a claim based on its lack of novelty. It simply is not relevant or material to that point. [*544] Therefore, since we do not know what additional evidence appellants might have been able to present if their claims had been rejected under § 103, it would not be proper for us to conjecture whether such a rejection [**16] might be sustained.

For the foregoing reasons, the rejection of claims 1 and 10 under 35 USC 112 is affirmed, and the rejection of claims 1, 2 and 10 under 35 USC 102(b) is reversed.

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tries, Inc. v. Cardinal IG Company, 239 F.3d 1239, 1245, 57 USPQ2d 1776, 1780-81 (Fed. Cir. 2001) (based on specification and other evidence, "composed of" interpreted in same manner as "consisting essentially of"); *In re Bertsch*, 132 F.2d 1014, 1019-20, 56 USPQ 379, 384 (CCPA 1942) ("Composed of" interpreted in same manner as "consisting of"; however, court further remarked that "the words 'composed of' may under certain circumstances be given, in patent law, a broader meaning than 'consisting of.'").

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2111.04 "Adapted to," "Adapted for," "Wherein," and "Whereby" Clauses [R-3]

Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;
(B) "wherein" clauses; and
(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Id.* However, the court noted (quoting *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" *Id.*<

2112 Requirements of Rejection Based on Inherency; Burden of Proof [R-3]

The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

I. SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). >In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court held that the claimed promoter sequence obtained by sequencing a prior art plasmid that was not previously sequenced was anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. The court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." *Id.*< See also MPEP § 2112.01 with regard to inherency and product-by-process claims and MPEP § 2141.02 with regard to inherency and rejections under 35 U.S.C. 103.

II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allow-

ing expert testimony with respect to post-critical date clinical trials to show inherency); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999) ("If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics."); *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known.")>; *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)<.

III. A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

IV. EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.). >Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.<

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients). The examiner applied a U.S. patent to Schjeldahl which disclosed injection molding a tubular preform and then injecting air into the preform to expand it against a mold (blow molding). The reference did not directly state that the end product balloon was biaxially oriented. It did disclose that the balloon was "formed from a thin flexible inelastic, high tensile strength, biaxially oriented synthetic plastic material." *Id.* at 1462 (emphasis in original). The examiner argued that Schjeldahl's balloon was inherently biaxially oriented. The Board reversed on the basis that the examiner did not provide objective evidence or cogent technical reasoning to support the conclusion of inherency.).

In *In re Schreiber*, 128 F.3d 1473, 44 USPQ2d 1429 (Fed. Cir. 1997), the court affirmed a finding that a prior patent to a conical spout used primarily to dispense oil from an oil can inherently performed the functions recited in applicant's claim to a conical container top for dispensing popped popcorn. The examiner had asserted inherency based on the structural similarity between the patented spout and applicant's disclosed top, i.e., both structures had the same general shape. The court stated:

> [N]othing in Schreiber's [applicant's] claim suggests that Schreiber's container is of a 'different shape' than Harz's [patent]. In fact, [ ] an embodiment according to Harz (Fig. 5) and the embodiment depicted in Fig. 1 of Schreiber's application have the same general shape. For that reason, the examiner was justified in concluding that the opening of a conically shaped top as disclosed by Harz is inherently of a size sufficient to 'allow [ ] several kernels of popped popcorn to pass through at the same time' and that the taper of Harz's conically shaped top is inherently of such a shape 'as to by itself jam up the popped popcorn before the end of the cone and permit the dispensing of only a few kernels at a shake of a package when the top is mounted to the container.' The examiner therefore correctly found that Harz established a prima facie case of anticipation.

In re Schreiber, 128 F.3d at 1478, 44 USPQ2d at 1432.

V. ONCE A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on '*prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

In *In re Fitzgerald*, the claims were directed to a self-locking screw-threaded fastener comprising a metallic threaded fastener having patches of crystallizable thermoplastic bonded thereto. The claim further specified that the thermoplastic had a reduced degree of crystallization shrinkage. The specification disclosed that the locking fastener was made by heating the metal fastener to melt a thermoplastic blank which is pressed against the metal. After the thermoplastic adheres to the metal fastener, the end product is cooled by quenching in water. The examiner made a rejection based on a U.S. patent to Barnes. Barnes taught a self-locking fastener in which the patch of thermoplastic was made by depositing thermoplastic powder on a metallic fastener which was then heated. The end product was cooled in ambient air, by cooling air or by contacting the fastener with a water trough. The court first noted that the two fasteners were identical or only slightly different from each other. "Both fasteners possess the same utility, employ the same crystallizable polymer (nylon 11), and have an adherent plastic patch formed by melting and then cooling the polymer." *Id.* at 596 n.1, 619 F.2d at 70 n.1. The court then noted that the Board had found that Barnes'

cooling rate could reasonably be expected to result in a polymer possessing the claimed crystallization shrinkage rate. Applicants had not rebutted this finding with evidence that the shrinkage rate was indeed different. They had only argued that the crystallization shrinkage rate was dependent on the cool down rate and that the cool down rate of Barnes was much slower than theirs. Because a difference in the cool down rate does not necessarily result in a difference in shrinkage, objective evidence was required to rebut the 35 U.S.C. 102/103 *prima facie* case.

In *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429, 1432 (Fed.Cir.1997), the court held that applicant's declaration failed to overcome a *prima facie* case of anticipation because the declaration did not specify the dimensions of either the dispensing top that was tested or the popcorn that was used. Applicant's declaration merely asserted that a conical dispensing top built according to a figure in the prior art patent was too small to jam and dispense popcorn and thus could not inherently perform the functions recited in applicant's claims. The court pointed out the disclosure of the prior art patent was not limited to use as an oil can dispenser, but rather was broader than the precise configuration shown in the patent's figure. The court also noted that the Board of Patent Appeals and Interferences found as a factual matter that a scaled-up version of the top disclosed in the patent would be capable of performing the functions recited in applicant's claim.

See MPEP § 2113 for more information on the analogous burden of proof applied to product-by-process claims.

2112.01 Composition, Product, and Apparatus Claims [R-3]

I. PRODUCT AND APPARATUS CLAIMS — WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best,* 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Claims were directed to a titanium alloy containing 0.2-0.4% Mo and 0.6-0.9% Ni having corrosion resistance. A Russian article disclosed a titanium alloy containing 0.25% Mo and 0.75% Ni but was silent as to corrosion resistance. The Federal Circuit held that the claim was anticipated because the percentages of Mo and Ni were squarely within the claimed ranges. The court went on to say that it was immaterial what properties the alloys had or who discovered the properties because the composition is the same and thus must necessarily exhibit the properties.).

See also *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971) (Claim 1 was directed to a parachute canopy having concentric circumferential panels radially separated from each other by radially extending tie lines. The panels were separated "such that the critical velocity of each successively larger panel will be less than the critical velocity of the previous panel, whereby said parachute will sequentially open and thus gradually decelerate." The court found that the claim was anticipated by Menget. Menget taught a parachute having three circumferential panels separated by tie lines. The court upheld the rejection finding that applicant had failed to show that Menget did not possess the functional characteristics of the claims.); *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) (A patent to a pencil for cleaning fingernails was held invalid because a pencil of the same structure for writing was found in the prior art.).

II. COMPOSITION CLAIMS — IF THE COMPOSITION IS PHYSICALLY THE SAME, IT MUST HAVE THE SAME PROPERTIES

"Products of identical chemical composition can not have mutually exclusive properties." A chemical

composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a *prima facie* case of unpatentability of Spada's polymer latexes for lack of novelty.").

III. PRODUCT CLAIMS – NONFUNCTIONAL PRINTED MATTER DOES NOT DISTINGUISH CLAIMED PRODUCT FROM OTHERWISE IDENTICAL PRIOR ART PRODUCT

Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, **>367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004)< (Claim at issue was a kit requiring instructions and a buffer agent. The Federal Circuit held that the claim was anticipated by a prior art reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.). See also *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983)("Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability....[T]he critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate.").

2112.02 Process Claims

PROCESS CLAIMS — PRIOR ART DEVICE ANTICIPATES A CLAIMED PROCESS IF THE DEVICE CARRIES OUT THE PROCESS DURING NORMAL OPERATION

Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. *In re King*, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986) (The claims were directed to a method of enhancing color effects produced by ambient light through a process of absorption and reflection of the light off a coated substrate. A prior art reference to *Donley* disclosed a glass substrate coated with silver and metal oxide 200-800 angstroms thick. While Donley disclosed using the coated substrate to produce architectural colors, the absorption and reflection mechanisms of the claimed process were not disclosed. However, King's specification disclosed using a coated substrate of Donley's structure for use in his process. The Federal Circuit upheld the Board's finding that "Donley inherently performs the function disclosed in the method claims on appeal when that device is used in 'normal and usual operation' " and found that a *prima facie* case of anticipation was made out. *Id.* at 138, 801 F.2d at 1326. It was up to applicant to prove that Donley's structure would not perform the claimed method when placed in ambient light.). See also *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) (Applicant claimed a process for preparing a hydrolytically-stable zeolitic aluminosilicate which included a step of "cooling the steam zeolite ... at a rate sufficiently rapid that the cooled zeolite exhibits a X-ray diffraction pattern ...." All the process limitations were expressly disclosed by a U.S. patent to Hansford except the cooling step. The court stated that any sample of Hansford's zeolite would necessarily be cooled to facilitate subsequent handling. Therefore, a *prima facie* case under 35 U.S.C. 102/103 was made. Applicant had failed to introduce any evidence comparing X-ray diffraction patterns showing a difference in cooling rate between the claimed process and that of Hansford or any data showing that the process of Hansford would result in a product with a different X-ray diffraction. Either type of evidence would have rebutted the *prima facie* case under 35 U.S.C. 102. A further analysis would be necessary to determine if the process was unobvious under 35 U.S.C. 103.); *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating

Evidence Appendix (B)

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707.07(f) Answer All Material Traversed [R-3] - 700 Examination of Applications

707.07(f) Answer All Material Traversed [R-3]

In order to provide a complete application file history and to enhance the clarity of the prosecution history record, an examiner must provide clear explanations of all actions taken by the examiner during prosecution of an application.

Where the requirements are traversed, or suspension thereof requested, the examiner should make proper reference thereto in his or her action on the amendment.

Where the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it.

If applicant's arguments are persuasive and upon reconsideration of the rejection, the examiner determines that the previous rejection should be withdrawn, the examiner must provide in the next Office communication the reasons why the previous rejection is withdrawn by referring specifically to the page(s) and line(s) of applicant's remarks which form the basis for withdrawing the rejection. It is not acceptable for the examiner to merely indicate that all of applicant's remarks form the basis for withdrawing the previous rejection. Form paragraph **7.38.01** may be used. If the withdrawal of the previous rejection results in the allowance of the claims, the reasons, which form the basis for the withdrawal of the previous rejection, may be included in a reasons for allowance. See MPEP § **1302.14**. If applicant's arguments are persuasive and the examiner determines that the previous rejection should be withdrawn but that, upon further consideration, a new ground of rejection should be made, form paragraph **7.38.02** may be used. See MPEP § **706.07(a)** to determine whether the Office action may be made final.

If a rejection of record is to be applied to a new or amended claim, specific identification of that ground of rejection, as by citation of the paragraph in the former Office letter in which the rejection was originally stated, should be given.

ANSWERING ASSERTED ADVANTAGES

After an Office action, the reply (in addition to making amendments, etc.) may frequently include arguments and affidavits to the effect that the prior art cited by the examiner does not teach how to obtain or does not inherently yield one or more advantages (new or improved results, functions or effects), which advantages are urged to warrant issue of a patent on the allegedly novel subject matter claimed.

If it is the examiner's considered opinion that the asserted advantages are not sufficient to overcome the rejection(s) of record, he or she should state the reasons for his or her position in the record, preferably in the action following the assertion or argument relative to such advantages. By so doing the applicant will know that the asserted advantages have actually been considered by the examiner and, if appeal is taken, the Board of Patent Appeals and Interferences will also be advised. See **MPEP § 716** *et seq.* for the treatment of affidavits and declarations under **37 CFR 1.132**.

The importance of answering applicant's arguments is illustrated by *In re Herrmann*, 261 F.2d 598, 120 USPQ 182 (CCPA 1958) where the applicant urged that the subject matter claimed produced new and useful results. The court noted that since applicant's statement of advantages was not questioned by the examiner or the Board of Appeals, it was constrained to accept the statement at face value and therefore found certain claims to be allowable. See also *In re Soni*, 54 F.3d 746, 751, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) (Office failed to rebut applicant's argument).

Form paragraphs **7.37** through **7.37.13** may be used where applicant's arguments are not persuasive.

Form paragraphs **7.38** through **7.38.02** may be used where applicant's arguments are moot or persuasive.

¶ 7.37 Arguments Are Not Persuasive

Applicant's arguments filed **[1]** have been fully considered but they are not persuasive. **[2]**

Examiner Note

1. The examiner must address all arguments which have not already been responded to in the statement of the rejection.

2. In bracket 2, provide explanation as to non-persuasiveness.

¶ 7.38 Arguments Are Moot Because of New Ground(s) of Rejection

Applicant's arguments with respect to claim **[1]** have been considered but are moot in view of the new ground(s) of rejection.

Examiner Note

The examiner must, however, address any arguments presented by the applicant which are still relevant to any references being applied.

¶ 7.38.01 Arguments Persuasive, Previous Rejection/Objection Withdrawn

Applicant's arguments, see [**1**], filed [**2**], with respect to [**3**] have been fully considered and are persuasive. The [**4**] of [**5**] has been withdrawn.

Examiner Note

1. In bracket 1, identify the page(s) and line number(s) from applicant's remarks which form the basis for withdrawing the previous rejection/objection.

2. In bracket 3, insert claim number, figure number, the specification, the abstract, etc.

3. In bracket 4, insert rejection or objection.

4. In bracket 5, insert claim number, figure number, the specification, the abstract, etc.

¶ 7.38.02 Arguments Persuasive, New Ground(s) of Rejection

Applicant's arguments, see [**1**], filed [**2**], with respect to the rejection(s) of claim(s) [**3**] under [**4**] have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of [**5**].

Examiner Note

1. In bracket 1, identify the page(s) and line number(s) from applicant's remarks which form the basis for withdrawing the previous rejection.

2. In bracket 3, insert the claim number(s).

3. In bracket 4, insert the statutory basis for the previous rejection.

4. In bracket 5, insert the new ground(s) of rejection, e.g., different interpretation of the previously applied reference, newly found prior art reference(s), and provide an explanation of the rejection.

¶ 7.37.01 Unpersuasive Argument: Age of Reference(s)

In response to applicant's argument based upon the age of the references, contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

Examiner Note

This form paragraph must be preceded by form paragraph 7.37.

¶ 7.37.02 Unpersuasive Argument: Bodily Incorporation

In response to applicant's argument that **[1]**, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Examiner Note

1. In bracket 1, briefly restate applicant's arguments with respect to the issue of bodily incorporation.

2. This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.03 Unpersuasive Argument: Hindsight Reasoning

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Examiner Note

This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.04 Unpersuasive Argument: No Suggestion To Combine

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, **[1]**.

Examiner Note

1. In bracket 1, explain where the motivation for the rejection is found, either in the references, or in the knowledge generally available to one of ordinary skill in the art.

2. This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.05 Unpersuasive Argument: Nonanalogous Art

In response to applicant's argument that **[1]** is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, **[2]**.

Examiner Note

1. In bracket 1, enter the name of the reference which applicant alleges is nonanalogous.

2. In bracket 2, explain why the reference is analogous art.

3. This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.06 Unpersuasive Argument: Number of References

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Examiner Note

This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.07 Unpersuasive Argument: Applicant Obtains Result Not Contemplated by Prior Art

In response to applicant's argument that **[1]**, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Examiner Note

1. In bracket 1, briefly restate applicant's arguments with respect to the issue of results not contemplated by the prior art.

2. This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.08 Unpersuasive Argument: Arguing Limitations Which Are Not Claimed

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., **[1]**) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Examiner Note

1. In bracket 1, recite the features upon which applicant relies, but which are not recited in the claim(s).

2. This form paragraph must be preceded by form paragraph **7.37**.

**>

¶ 7.37.09 Unpersuasive Argument: Intended Use

In response to applicant's argument that **[1]**, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Examiner Note

1. In bracket 1, briefly restate applicant's arguments with respect to the issue of intended use.

2. This form paragraph must be preceded by form paragraph **7.37**.

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¶ 7.37.10 Unpersuasive Argument: Limitation(s) in Preamble

In response to applicant's arguments, the recitation **[1]** has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Examiner Note

1. In bracket 1, briefly restate the recitation about which applicant is arguing.

2. This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.11 Unpersuasive Argument: General Allegation of Patentability

Applicant's arguments fail to comply with **37 CFR 1.111(b)** because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the

references.

Examiner Note

This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.12 Unpersuasive Argument: Novelty Not Clearly Pointed Out

Applicant's arguments do not comply with **37 CFR 1.111(c)** because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

Examiner Note

This form paragraph must be preceded by form paragraph **7.37**.

¶ 7.37.13 Unpersuasive Argument: Arguing Against References Individually

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Examiner Note

This form paragraph must be preceded by form paragraph **7.37**.

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Evidence Appendix (B)

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904 How to Search [R-5] - 900 Prior Art, Classification, and Search

904 How to Search [R-5]

The examiner, after having obtained a thorough understanding of the invention disclosed and claimed in the nonprovisional application, then searches the prior art as disclosed in patents and other published documents, i.e., nonpatent literature (NPL). Any document used in the rejection of a claim is called a reference. An inventor name search should be made to identify other applications and/or patents which may be applicable as references for double patenting rejections. See MPEP § **804**.

In all continuing applications, the parent applications should be reviewed by the examiner for pertinent prior art. Where the cited prior art of a parent application has been reviewed, this fact should be made of record in accordance with the procedure set forth at paragraph II.(E) of **MPEP § 719.05**. For national stage applications filed under 35 U.S.C. **371**, the examiner will consider the documents cited in an international search report when the Form PCT/DO/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage application file. See MPEP § **609.03**.

The first search should be such that the examiner need not ordinarily make a second search of the prior art, unless necessitated by amendments to the claims by the applicant in the first reply, except to check to determine whether any reference which would appear to be substantially more pertinent than the prior art cited in the first Office action has become available subsequent to the initial prior art search. The first search should cover the invention as described and claimed, including the inventive concepts toward which the claims appear to be directed. It should not be extended merely to add immaterial variants.

In the first action on the merits of an application, the examiner must complete the Image File Wrapper (IFW) search notes form in *>the Office Action Correspondence Subsystem (OACS)< to include the classes and subclasses of domestic and foreign patents, abstract collections, and publications in which the search for prior art was made. Other information collections and sources in which the search for prior art was made must also be identified by the examiner. The examiner must also indicate the date(s) on which the search was conducted. Note MPEP § **719.05**.

In subsequent actions, where the search is brought **>up-to-date< and/or where a further search is made, the examiner must indicate on the IFW search notes form that the search has been updated and/or identify the additional field of search. See MPEP § **719.05**. Any search updates should include all of the relevant or pertinent databases and the search queries and classifications employed in the original search.

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Evidence Appendix (B)

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1207.04 Reopening of Prosecution After Appeal [R-8] - 1200 Appeal

1207.04 Reopening of Prosecution After Appeal [R-8]

The examiner may, with approval from the supervisory patent examiner, reopen prosecution to enter a new ground of rejection after appellant's brief or reply brief has been filed. The Office action containing a new ground of rejection may be made final if the new ground of rejection was (A) necessitated by amendment, or (B) based on information presented in an information disclosure statement under **37 CFR 1.97(c)** where no statement under 37 CFR **1.97**(e) was filed. See **MPEP § 706.07(a)**. Any after final amendment or affidavit or other evidence that was not entered before must be entered and considered on the merits.

Form paragraph 12.187 may be used when reopening prosecution:

**>

¶ 12.187 Reopening of Prosecution After Appeal Brief or Reply Brief

In view of the **[1]** filed on **[2]**, PROSECUTION IS HEREBY REOPENED. **[3]** set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR **1.111** (if this Office action is non-final) or a reply under 37 CFR **1.113** (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR **41.31 followed by an appeal brief under 37 CFR 41.37**. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in **37 CFR 41.20** have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by

signing below:

[4]

Examiner Note:

1. In bracket 1, insert --appeal brief--, --supplemental appeal brief--, --reply brief-- or --supplemental reply brief--.

2. In bracket 2, insert the date on which the brief was filed.

3. In bracket 3, insert --A new ground of rejection is-- or --New grounds of rejection are--.

4. In bracket 4, insert the SPE's signature. Approval of the SPE is required to reopen prosecution after an appeal. See MPEP §§ **1002.02(d)** and **1207.04**.

5. Use this form paragraph to reopen prosecution in order to make a new ground of rejection of claims. The Office action following a reopening of prosecution may be made final if all new grounds of rejection were either (A) necessitated by amendment or (B) based on information presented in an information disclosure statement under 37 CFR **1.97**(c) where no statement under 37 CFR **1.97**(e) was filed. See MPEP § **706.07(a)**.

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After reopening of prosecution, appellant must exercise one of the following options to avoid abandonment of the application:

(A) file a reply under **37 CFR 1.111**, if the Office action is non-final;

(B) file a reply under **37 CFR 1.113**, if the Office action is final; or

(C) initiate a new appeal by filing a new notice of appeal under 37 CFR **41.31**.

If appellant elects to continue prosecution and prosecution was reopened prior to a decision on the merits by the Board of Patent Appeals and Interferences, the fee paid for the notice of appeal, appeal brief, and request for oral hearing (if applicable) will be applied to a later appeal on the same application. If, however, the appeal fees set forth in 37 CFR **41.20** have increased since they were previously paid, applicant must pay the difference between the increased fees and the amount previously paid. If appellant elects to initiate a new appeal by filing a notice of appeal, appellant must file a complete new brief in compliance with the 37 CFR **41.37 within two months from the filing of the new notice of appeal.** See MPEP § **1204.01** for more information on reinstatement of an appeal.

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Evidence Appendix (B)

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706.07(a) Final Rejection, When Proper on Second Action [R-6] - 700 Examination of Applications

706.07(a) Final Rejection, When Proper on Second Action [R-6]

Due to the change in practice as affecting final rejections, older decisions on questions of prematureness of final rejection or admission of subsequent amendments do not necessarily reflect present practice.

Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in **37 CFR 1.97(c)** with the fee set forth in **37 CFR 1.17(p)**. Where information is submitted in an information disclosure statement during the period set forth in **37 CFR 1.97(c)** with a fee, the examiner may use the information submitted, e.g., a printed publication or evidence of public use, and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner. See **MPEP § 609.04**(b). Furthermore, a second or any subsequent action on the merits in any application or patent undergoing reexamination proceedings will not be made final if it includes a rejection, on newly cited art, other than information submitted in an information disclosure statement filed under **37 CFR 1.97(c)** with the fee set forth in **37 CFR 1.17**(p), of any claim not amended by applicant or patent owner in spite of the fact that other claims may have been amended to require newly cited art. Where information is submitted in a reply to a requirement under 37 CFR **1.105**, the examiner may NOT make the next Office action relying on that art final unless all instances of the application of such art are necessitated by amendment.

A second or any subsequent action on the merits in any application or patent involved in reexamination proceedings should not be made final if it includes a rejection, on prior art not of record, of any claim amended to include limitations which should reasonably have been expected to be claimed. See **MPEP § 904** *et seq.* **>However, note that an examiner cannot be expected to foresee whether or how an

applicant will amend a claim to overcome a rejection except in very limited circumstances (e.g., where the examiner suggests how applicant can overcome a rejection under 35 U.S.C. **112**, second paragraph)<.

A second or any subsequent action on the merits in any application or patent involved in reexamination proceedings may not be made final if it contains a new ground of rejection necessitated by the amendments to 35 U.S.C. **102**(e) by the Intellectual Property and High Technology Technical Amendments Act of 2002 (Pub. L. 107-273, 116 Stat. 1758 (2002)), unless the new ground of rejection was necessitated by an amendment to the claims or as a result of information submitted in an information disclosure statement under **37 CFR 1.97(c)** with the fee set forth in **37 CFR 1.17(p)**.

When applying any 35 U.S.C. **102**(e)/ **103** references against the claims of an application the examiner should anticipate that a statement averring common ownership at the time the invention was made may disqualify any patent or application applied in a rejection under 35 U.S.C. **103** based on 35 U.S.C. **102**(e). If such a statement is filed in reply to the 35 U.S.C. **102**(e)/ **103** rejection and the claims are not amended, the examiner may not make the next Office action final if a new rejection is made. See MPEP § **706.02**(l)(3). If a reference is disqualified under the joint research agreement provision of 35 U.S.C. **103**(c) and a new subsequent double patenting rejection based upon the disqualified reference is applied, the next Office action, which contains the new double patenting rejection, may be made final even if applicant did not amend the claims (provided that the examiner introduces no other new ground of rejection that was not necessitated by either amendment or an information disclosure statement filed during the time period set forth in 37 CFR **1.97**(c) with the fee set forth in 37 CFR **1.17**(p)). The Office action is properly made final because the new double patenting rejection was necessitated by amendment of the application by applicant.

See **MPEP § 809.02(a)** for actions which indicate generic claims as not allowable.

In the consideration of claims in an amended case where no attempt is made to point out the patentable novelty, the examiner should be on guard not to allow such claims. See **MPEP § 714.04**. The claims may be finally rejected if, in the opinion of the examiner, they are clearly open to rejection on grounds of record.

Form paragraph **7.40** should be used where an action is made final including new grounds of rejection necessitated by applicant's amendment.

¶ 7.40 Action Is Final, Necessitated by Amendment

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See **MPEP § 706.07(a)**. Applicant is reminded of the extension of time policy as set forth in **37 CFR 1.136(a)**.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to **37 CFR 1.136(a)** will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Examiner Note

1. This form paragraph should **not** be used in reissue litigation cases (SSP- 1 month) or in reexamination proceedings (SSP- 1 or 2 months).

2. **37 CFR 1.136(a)** should not be available in a reissue litigation case and is not available in reexamination proceedings.

¶ 7.40.01 Action Is Final, Necessitated by IDS With Fee

Applicant's submission of an information disclosure statement under **37 CFR 1.97(c)** with the fee set forth in **37 CFR 1.17(p)** on **[1]** prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § **609.04(b)**. Applicant is reminded of the extension of time policy as set forth in **37 CFR 1.136(a)**.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to **37 CFR 1.136(a)** will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Examiner Note

1. This form paragraph should **not** be used and a final rejection is improper where there is another new ground of rejection introduced by the examiner which was not necessitated by amendment to the claims.

2. In bracket 1, insert the filing date of the information disclosure statement containing the identification of the item of information used in the new ground of rejection.

¶ 7.40.02 Action Is Final, Necessitated by Invoking the Joint Research Agreement Prior Art Exclusion Under 35 U.S.C. 103(c)

Applicant's submission of the requirements for the joint research agreement prior art exclusion under **35 U.S.C. 103**(c) on **[1]** prompted the new double patenting rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See **MPEP § 706.02**(l)(3). Applicant is reminded of the extension of time policy as set forth in **37 CFR 1.136**(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Examiner Note

1. This form paragraph should not be used and a final rejection is improper where there is another new ground of rejection introduced by the examiner which was not necessitated by amendment to the claims nor based on information submitted in an information disclosure statement filed during the period set forth in **37 CFR 1.97**(c) with the fee set forth in **37 CFR 1.17**(p).

2. In bracket 1, insert the filing date of the submission of the requirements for the joint research agreement prior art exclusion under **35 U.S.C. 103**(c).

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Evidence Appendix (B)

browse before

707.07 Completeness and Clarity of Examiner's Action - 700 Examination of Applications

707.07 Completeness and Clarity of Examiner's Action

37 CFR 1.104 Nature of examination.

*****

(b) *Completeness of examiner's action.* The examiner's action will be complete as to all matters, except that in appropriate circumstances, such as misjoinder of invention, fundamental defects in the application, and the like, the action of the examiner may be limited to such matters before further action is made. However, matters of form need not be raised by the examiner until a claim is found allowable.

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707.07(e) Note All Outstanding Requirements - 700 Examination of Applications

707.07(e) Note All Outstanding Requirements

In taking up an amended application for action the examiner should note in every letter all the requirements outstanding against the application. Every point in the prior action of an examiner which is still applicable must be repeated or referred to, to prevent the implied waiver of the *requirement*. Such requirements include requirements for information under 37 CFR **1.105** and MPEP § **704.10**; however the examiner should determine whether any such requirement has been satisfied by a negative reply under 37 CFR **1.105(a)(3)**.

As soon as allowable subject matter is found, correction of all informalities then present should be *required*.

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EVIDENCE APPENDIX(C)

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§ 1.97 Filing of information disclosure statement. - Appendix R Patent Rules

§ 1.97 Filing of information disclosure statement.

(a) In order for an applicant for a patent or for a reissue of a patent to have an information disclosure statement in compliance with § **1.98** considered by the Office during the pendency of the application, the information disclosure statement must satisfy one of paragraphs (b), (c), or (d) of this section.

(b) An information disclosure statement shall be considered by the Office if filed by the applicant within any one of the following time periods:

(1) Within three months of the filing date of a national application other than a continued prosecution application under § **1.53(d)**;

(2) Within three months of the date of entry of the national stage as set forth in § **1.491** in an international application;

(3) Before the mailing of a first Office action on the merits; or

(4) Before the mailing of a first Office action after the filing of a request for continued examination under § **1.114**.

(c) An information disclosure statement shall be considered by the Office if filed after the period specified in paragraph (b) of this section, provided that the information disclosure statement is filed before the mailing date of any of a final action under § **1.113**, a notice of allowance under § **1.311**, or an action that otherwise closes prosecution in the application, and it is accompanied by one of:

(1) The statement specified in paragraph (e) of this section; or

(2) The fee set forth in § **1.17(p)**.

(d) An information disclosure statement shall be considered by the Office if filed by the applicant after the period specified in paragraph (c) of this section, provided that the information disclosure statement is filed on or before payment of the issue fee

and is accompanied by:

(1) The statement specified in paragraph (e) of this section; and

(2) The fee set forth in § **1.17(p)**.

(e) A statement under this section must state either:

(1) That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

(2) That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § **1.56(c)** more than three months prior to the filing of the information disclosure statement.

(f) No extensions of time for filing an information disclosure statement are permitted under **§ 1.136**. If a *bona fide* attempt is made to comply with **§ 1.98**, but part of the required content is inadvertently omitted, additional time may be given to enable full compliance.

(g) An information disclosure statement filed in accordance with this section shall not be construed as a representation that a search has been made.

(h) The filing of an information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in **§ 1.56**(b).

(i) If an information disclosure statement does not comply with either this section or § **1.98**, it will be placed in the file but will not be considered by the Office.

[48 FR 2712, Jan. 20, 1983, effective date Feb. 27, 1983; 57 FR 2021, Jan. 17, 1992, effective Mar. 16, 1992; para. (d) revised, 60 FR 20195, Apr. 25, 1995, effective June 8, 1995; paras. (a)- (d) revised, 61 FR 42790, Aug. 19, 1996, effective Sept. 23, 1996; paras. (c)-(e) revised, 62 FR 53131, Oct. 10, 1997, effective Dec. 1, 1997; para. (b) revised, 65 FR 14865, Mar. 20, 2000, effective May 29, 2000 (adopted as final, 65 FR 50092, Aug. 16, 2000); paras. (a) through (e) and (i) revised, 65 FR 54604, Sept. 8, 2000, effective Nov. 7, 2000]

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NEW TRITERPENOIDS FROM *NAPOLEONEA IMPERIALIS*

[Triterpenoides nouveaux de *Napoleonaea imperialis*]

Meuza Kapundu et al.

Phytochemistry

Vol. 19

1980

pp. 615-622

(Received July 23, 1979)

Key Word Index—*Napoleonaea imperialis*; Lecythidaceae; prosapogenin: 21β-[6-deoxy-3,4-diangelate-β-glucopyranosyl]oxy3β,16α,22α,24,28-pentahydroxy-olean-12-ene; sapogenols; protoaescigenin; napoleogenol.

Abstract—Besides protoaescigenin, the seed saponin of *Napoleonaea imperialis* yields on hydrolysis a new sapogenol. Its structure has been deduced from spectral data. Controlled hydrolysis of this saponin yielded a new prosapogenin, the structure of which has been established. The names napoleogenol and napoleogenin are respectively proposed for the sapogenol and prosapogenin.

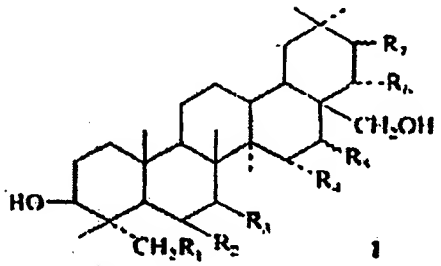
INTRODUCTION

/615*

The triterpenoids contained in five species of Lecythidaceae were the subject of an in-depth chemical study: the following triterpenes were isolated: careyagenols - A (**1b**), -B(**1f**), -C(**2**), -D(**1g**), E(**1h**) from *Careya arborea* [1, 2]; barringtogenols -B(**1a**), -C(**1b** = careyagenol-A), -D(**2** = careyagenol-C), E(**1j**) from *Barringtonia acutangula* [3-6]; tanginol (1i) from *B. acutangula* [7]; camelliagenin-A(**1c**) from *B. butonica* [8]; A_1-barrigenol (**1d**) from *B. butonica* [8] and *B. asiatica* [9]; R_1-barrigenol (**1e**) from *B.*

* The number in the margin indicates the pagination of the foreign text.

racemosa [9]; acutangulic acid (3c), barrinic acid (**3a**), barrigenic acid (**3b**) from *B. acutangula* [10-12]; barringtogenol (**3c**), barringtogenic acid (**3d**) from *B. racemosa* [13].

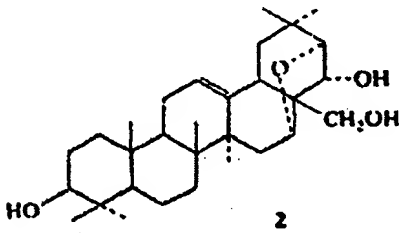


1

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Δ
1a	H	H	H	H	α-OR	OH	β-OH	12
1b	H	H	H	H	α-OH	OH	β-OH	12
1c	H	H	H	H	α-OH	OH	H	12
1d	H	H	H	OH	α-OH	OH	H	12
1e	H	H	H	OH	α-OH	OH	β-OH	12
1f	H	H	H	H	H	OH	β-OH	12
1g	H	H	H	H	H	OH	α-OH	12; 15
1h	H	H	H	H	H	OH	β-OH	11; 13-18
1i	OH	OH	OH	H	β-OH	H	H	12
1j	R	H	H	H	α-OH	OX	β-OX	12

R = Angeloyle, X = benzoyle.

R = angeloyl, X = benzoyl



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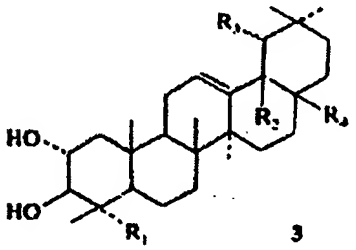


3

	R_1	R_2	R_3	R_4
3a	COOH	H	α-OH	COOH
3b	COOH	H	β-OH	COOH
3c	Me	OH	H	COOH
3d	COOH	H	H	COOH
3e	CH_2OH	H	H	CH_2OH

Here we are reporting the results of our recent research on the saponin extracted from seeds of *Napoleonaea imperialis* Beauv. (Lecythidaceae). The sample analyzed was harvested at the Kisantu Botanical Garden (Zaire). It is authenticated by the herbarium exsiccatum H. Breyne deposited at the Brussels National Botanical Garden.

RESULTS AND DISCUSSION

The ground seeds of *Napoleonea imperialis* are extracted with MeOH. The addition of Et_2O to the methanolic extract precipitates the saponin which is separated by filtration and then hydrolyzed by 3.5% $HClO_4$. The precipitate obtained during hydrolysis is acetylated. High pressure liquid chromatography (HPLC) followed by crystallization provided three products (A, B, C) in the pure state. A (**8**), MP: 204-206 ° (MeOH); $[\alpha]_D$ 45.4 ° ($CHCl_{[illegible]}$, c 0.03); λ^{MeOH}_{max} nm (log ε): 215 (4.26); MS m/e 699 (0.1%), 519 (5) 403 (1) (699-4 OAc-HAc), 353 (100), 253 (34), 228 (21), 153 (57), 83 (90), 55 (50);

NMR (see Tables 1 and 2). B(**9**), MP: 245-247 ° (MeOH), $[\alpha]_D$ 13.7 ° ($CHCl_{[illegible]}$ c 0.16); λ^{MeOH}_{max} nm (log ε): 215 (4.26); MS m/e 699 (1%), 639 (5), 519 (11),353 (100), 270 (16), 253(27), 211 (27), 153 (45), 83 (85), 55(60); NMR (see Tables 1 and 2), C (**10**) noncrystalline, MP: 185-187 °C; $[\alpha]_D$ 9.4 ° ($CHCl_3$ c 0.2); λ^{MeOH}_{max} nm (log ε); 216 (4.26); MS m/e 699 (0.4%), 519 (12),403 (10), 353 (100), 307 (10), 270 (21), 253(73), 153 (94), 83 (94), 55(80); NMR (see Tables 1 and 2).

TABLE 1. ^{1}H NMR parameters of compounds **8**(A), **9** (B) and **10** (C) /616

		12-H	16β-H	3α-H	4β-CH_2OAc	17β-CH_2OAc	21α-H 21β-H	Me
8 (A)	δ	5,35	5,35	4,58	4,37; 4,16	3,97; 3,84	3,83; 3,48	1,36(3H); 1,01(3H); 0,99(3H); 0,98(3H); 0,93(3H); 0,91(3H)
	MJ	φ	φ	φ	d, d (12)	d, d (10,9)	d, d (9,6)	φ s
9 (B)	δ	5,27	5,30	4,61	4,36; 4,13	3,72	3,74; 5,21	1,28(3H); 1,05(3H); 1,01(3H); 0,97(3H); 0,95(3H); 0,89(3H)
	MJ	φ	φ	φ	d, d (12)	s	d, d (10,0)	φ s
10 (C)	δ	5,36	4,17	4,60	4,38; 4,15	3,64	3,66; 5,31	1,41(3H); 1,03(3H); 0,98(3H); 0,92(3H); 0,89(3H)
	MJ	m	tm	φ	d, d (11,7)	s	d, d (9,7)	5 s

		OAc	A (5'-H)	M (5'-H)	X (5'-H)	N (2'-H)	Y (1'-H)	A^1_1 (5'-Me)
8 (A)	δ	2,04(3H); 2,03(3H); 2,02(3H); 2,01(3H)	5,39	5,01	3,67	5,13	4,55	1,26
	MJ	4 s	$^3J_{AN}$ = 10; $^3J_{AY}$ = 0	$^3J_{AM}$ = 9,6; $^3J_{MX}$ = 9,8	$m(J_{XA}; J_{XM})$ = 5,7	$\#(J_{AN} + J_{NY})$ = 17,9	$^3J_{NY}$ = 7,9	$^3J_{1'C}$ = 5,7
9 (B)	δ	2,10(3H); 2,05(3H); 2,03(3H); 2,01(3H)	5,24	4,99	3,56	4,98	4,55	1,26
	MJ	5 s	$^3J_{AN}$ = 9,7; $^3J_{AY}$ = 0	$^3J_{AM}$ = 9,7; $^3J_{MX}$ = 9,7	$m(J_{XA}; J_{XM})$ = 5,2	$^3J_{AN}$ = 9,7	$^3J_{NY}$ = 8,0	$^3J_{1'C}$ = 5,2
10 (C)	δ	2,07(3H); 2,04(3H); 2,04(3H)	5,32	4,97	3,60	5,00	4,57	1,26
	MJ	4 s	$^3J_{AN}$ = 9,7; $^3J_{AY}$ = 0	$^3J_{AM}$ = 9,7; $^3J_{MX}$ = 9,7	$m(J_{XA}; J_{XM})$ = 5,9	$^3J_{AN}$ = 9,7	$^3J_{NY}$ = 7,9	$^3J_{1'C}$ = 5,9

		A^2_1 A^2_2 (5'-H et 5''-H)	X^2_1 X^2_2 (5'-Me et 5''-Me)	Y^2_1 Y^2_2 (5'-Me et 5''-Me)
8 (A)	δ	6,05; 6,03	1,95	1,93
	MJ	m; m $^2J_{A_1A_2}$ = $^2J_{A'_1A'_2}$ = 6,6	m $^2J_{X_1X_2}$ = $^2J_{X'_1X'_2}$ = 1,4	m $^2J_{Y_1Y_2}$ = $^2J_{Y'_1Y'_2}$ = 1,4
9 (B)	δ	6,04	1,91	1,93
	MJ	m $^2J_{A_1A_2}$ = $^2J_{A'_1A'_2}$ = 7,0	m $^2J_{X_1X_2}$ = $^2J_{X'_1X'_2}$ = 1,4	m $^2J_{Y_1Y_2}$ = $^2J_{Y'_1Y'_2}$ = 1,3
10 (C)	δ	6,05; 6,03	1,91; 1,90	1,91; 1,79
	MJ	m; m $^2J_{A_1A_2}$ = $^2J_{A'_1A'_2}$ = 6,9	m; m $^2J_{X_1X_2}$ = $^2J_{X'_1X'_2}$ = 1,4	m; m $^2J_{Y_1Y_2}$ = $^2J_{Y'_1Y'_2}$ = 1,4

φ = recovery of signals, δ expressed in ppm and J in Hz, M = multiplicity (s = singlet; d = doublet; tm = poorly resolved triplet, part X of an ABX: m = multiplet); when they are present, the figures indicate the number of peaks observed in the spectrum.

From their physical constants, compounds A, B, C are not identified with any of the substances found in the Lecythidaceae during earlier studies [1-13]. The mass spectra and proton NMR and carbon-13 spectra lead us to propose a prosapogenin structure for A, B, C.

On the other hand, the treatment of the product of perchloric hydrolysis by a hydrochloric hydrolysis process leads to 2 products being obtained that after acetylation are isolated by fractionation on a silica gel column: E and F. E(**4**), MP: 203-205 ° (MeOH), $[\alpha]_D$ 63 ° ($CHCl_{[3]}$ c 0.14); λ^{MeOH}_{max} nm (log ε): 198 (3.93); MS M^+ m/e 658 (1%), 537 (7), 349 (16), 348 (68), 307 (10), 288 (62), 248 (32), 247 (16), 228 (100), 216 (15), 215 (87), 197 (42), 188 (81), 173 (27), 131 (26). F (**5**) noncrystalline, MP 127-130 ° ($CHCl_3$) $[\alpha]_D$ 30 ° ($CHCl_{[illegible]}$ c 0.05); λ^{MeOH}_{max} nm (log ε); 198 (3.96); MS M^+ m/e 716 (1%), 597 (12), 536 (12), 403 (7), 390 (15), 348 (15), 307 (15), 288 (15), 270 (33), 257 (60), 248 (24), 228 (42), 216 (25), 215 (100), 197 (89), 173 (39), 133 (37).

E has an empirical formula of $C_{38}H_{58}O_9$ determined by mass spectrometry (M^+ with m/e = 658) and elemental percent analysis. It is a derivative of Δ^{12}-oleanene: MS ions at 197, 215, 248, 307 MU created by fragmentation according to an inverse Diels-Alder reaction [14]; ^1H NMR, signal at δ 5.28 (t) due to the vinyl 12-H proton, ^{13}C NMR, δ 123.5; 141.9 ppm characteristic of double bonded C_{12} and C_{13} [15, 16]. The exam of the ^1H NMR chemical shifts induced by europium tris-dipivalomethanate [17, 18], $Eu(DPM)_3$, reveals that E contains 6 Me (δ 0.85 (3H, s); 0.95 (3H, s); 1.03 (6H, s); 1.09 (3H, s); 1.49 ppm (3H, 2) and 4 OAc (δ 1.03 ppm (12H, s)) [19]. Absorption at δ 4.60 ppm (1H, t ($J_{AX} = J_{BX}$) = 16 Hz) proves the presence of a 3β-OAc group [20]. In addition, the ^1H NMR presents two doublets at δ 4.11 and 3.80 ppm (J = 12 Hz) due to methylenic protons from a $-CH_2$-OAc group carried by the C_{17} [20, 21]. A pair of doublets appears δ 4.38 and 4.11 ppm (J = 12 Hz); it corresponds to the signal observed in the spectra of the acetylated derivatives of the compounds from the β-amyrine series such as protoaescigenin and camelliagenin-C, which is attributed to the methylenic protons of a $-CH_2OAc$ group

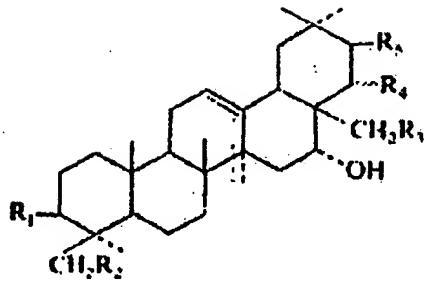
carried by the C_4 [22-24]. The ^1H NMR study of shifts induced by $Eu(DPM)_3$ shows that the $-CH_2OAc$ group carried by the C_4 is β oriented. The simultaneous appearance of a signal (poorly resolved triplet) at δ 4.36 ppm attributable to the 16-H proton and with an absorption at 1.49 ppm (3H, s) due to protons from the Me_{27} [25] gives evidence for an α substitution of the C_{15} by an OH function [26, 27]. A triplet (poorly resolved) is observed at δ 5.28 ppm (1H, part X of an ABX). By virtue of its position, it is comparable to that due to the 22β-H proton of the A1-barrigenol pentaacetate [9]. The superposition of signals due to 12-H and 22-H protons only enable confirmation that $J_{AX} + J_{BX}) < 10$ Hz, a value clearly less than that expected for the β-H epimer [9]. The discordance observed in ^{13}C NMR between the resonances of C_{26} and C_{27} of the camelliagenin-C pentaacetate ($\delta_{[illegible]}$ and $\delta_{[illegible]} = 72.1$ ppm) [28] and of compound E ($\delta_{c[illegible]}$ and $\delta_{c\,[illegible]} = 61.2$; 88.1 ppm) (Table 2) is in favor of the 22α-H configuration in E. The non-equivalence of methylenic protons of the C_{28} is more obvious in compound E ($\delta_A - \delta_B = 0.31$ ppm) than in the 3, 22, 23, 28 tetraacetate of camelligenin B ($\delta A - \delta_B = 0.21$ ppm) [24] and the 3, 22, 28 triacetate of camelligenin B (accidental equivalence $\delta A = \delta_B$ [23]. This difference, comparable to that existing between the protons of C_{24} ($\delta A - \delta_B = 0.27$ ppm) of the same molecule E, is connected to the presence on the C_{22} of a group with high anisotropy in the axial position [29]. /618

TABLE 2. Chemical shifts in C^{13} NMR /617

8 (A)	15,6	16,6	17,4	19,1	20,1	20,8	21,1	21,2
	21,9	22,6	23,6	26,7	29,3	30,6	33,3	36,2
	38,6	39,3	39,8	41,0	45,3	46,8	56,0	65,3(2)*
	69,6	70,8(2)	71,9	72,1	72,5	80,1(1)	91,2(1)	102,3(1)
	124,9(1)	126,9(1)	127,0(1)	139,0(1)	139,4(1)	140,0(1)	166,1	166,8
	168,5	169,0	170,5(2)	170,9				
9 (B)	15,8	16,9	18,1	19,4	19,5	20,5	21,0	21,4
	22,9	24,0	26,8	29,9	30,7	33,6	37,1	39,0
	40,0	40,4	41,2	41,4	45,1	46,5	46,6	47,0
	56,3	65,8	67,1	70,6	70,9	72,5	72,7	72,9
	73,2	80,4(1)	84,3(1)	102,3(1)	125,8(1)	127,5(2)	139,5(2)	139,8(1)
	166,6	167,3	168,9	170,2	170,9(3)	171,2		
10 (C)	15,5	16,8	17,9	18,9	19,4	20,2	20,7	20,9
	21,2	22,7	23,8	26,9	29,2	33,5	37,0	38,8
	40,0	40,4	41,3	45,8	47,0	56,3	65,4	66,9
	69,3	70,3	72,9	73,1(2)	73,3	80,3(1)	86,4(1)	102,0(1)
	124,5(1)	127,5(2)	138,4(2)	141,0(1)	166,4	167,0	168,6	169,6
	170,4(3)							
12 (H)	11,3	11,5	14,9	15,5	16,4	17,3	18,9	19,1
	20,9	21,9	22,5	23,7	26,1	26,2	29,3	36,2
	36,8	38,6	39,3	39,8	40,5	41,0	45,3	46,7
	46,8	56,0	65,0	65,5	69,6	71,4	71,9	72,7(2)
	80,1(1)	91,3	102,3	125,0(1)	139,9(1)	167,8	168,3(2)	170,0(2)
	174,2	175,1						
4 (E)	15,4	17,2	19,6	21,3	21,6	22,8	23,9	28,1
	29,4	30,5	32,6	37,1	38,7	40,4	40,7	41,3
	47,0	56,0	61,2	65,5	77,8	78,2	80,6	88,1
	123,5(1)	141,9(1)	170,1	170,4	170,5	170,8		
5 (F)	15,5	16,6	19,4	20,8	21,1	22,5	23,5	26,8
	28,8	33,2	33,4	35,5	36,8	38,6	39,7	40,4
	41,1	45,7	46,4	46,7	56,0	65,5	66,6	68,7
	73,9	78,4	80,1	124,7(1)	140,5(1)	170,0	170,5(2)	170,8(2)

* When they are present, the figures between parentheses indicate the number of carbon atoms characterized by the same δ.

The spectra have been recorded on a Brucker 22.63 MHz spectrometer. The samples were dissolved in $CHCl_3$ containing TMS as internal reference, δ expressed in ppm.



	R_1	R_2	R_3	R_4	R_5
4 (E)	OAc	OAc	OAc	β-OAc	H
5 (F)	OAc	OAc	OAc	α-OAc	OAc
6 (G)	OH	OH	OH	β-OH	H

All of this spectral data leads to proposing structure **4** for E. E is a tetraacetylated derivative of 3β,16α,22β,24,28-pentahydroxyolean-12-ene, new triterpene for which we propose the name napoleogenol.

F fulfills an empiric formula of $C_{40}H_{60}O_{11}$ (MS M+ with m/2 = 716). The mass spectra and ^1H NMR of F present analogies with those of E: MS ions at 197, 215, 248, 307, MU. ^1H NMR, δ 5.36 (1H, t) 12-H; 4.18 ppm, (1H, t poorly resolved) 16β-H; 1.45 (3H, s) Me27; 4.60 (t, $(J_{AX} + J_{BX})$ = 16 Hz) 3 α-H; 4.38, 4.12 ppm (d,d, J = 12 Hz) 4-CH_2OAc. The ^1H NMR study of the paramagnetic shifts induced by $Eu(DPM)_3$ [19] shows that F includes 5 OAc (δ 2.01 (3H, s); 2.93 (3H, s); 2.05 (9H,s) one of which is proteated by the C_{24} and 6 Me (δ 0.89 (6H, s); 0.98 (3H, s); 1.03 (3H, s); 1.06 (3H, s); 1.45 (3H, s)). ^1H NMR absorption at δ 3.66 ppm (2H, s with widened base) offers an explanation of the presence of a -CH_2OAc group in β position on the C_{17} [20, 23]. A pair of doublets at δ 5.56 and 5.39 ppm (J = 11 Hz) analogous to those created by 21α-H and 22β-H protons of jegosapogenol tetraacetate [20] and protoaescigenin pentaacetate [22] gives evidence of a transdiequatorial substitution of the C_{21} and C_{22} by 2 OAc. These spectral characteristics identify F with 3, 21, 22, 24, 28 pentaacetate of protoaescigenin (5).

The ^1H NMR spectrum of compound A has similarities with that of protoaescigenin pentaacetate (F). The following signals are found: δ 5.35 (1H, t) 12-H; 4.58 (5) 3α-H; 4.37, 4.16 (d, d, J = 12 Hz) 4-CH_2OAc. Furthermore, the ^1H NMR study of the δ induced by $Eu(DPM)_3$ [19] demonstrates that the orientation of the 4-CH_2OAc group is β. Dissimilarities are observed: the concomitant presence of a signal at δ 5.35 ppm (1H, t poorly resolved) attributable to the 16β-H proton [22] and of an absorption at δ 1.26 (3H, s) due to the protons of the Me_{27} indicates an α substitution of the C_{16} by an OAc [26, 27]. The ^1H NMR in the presence of $Eu(DPM)_3$ shows the existence of 7 Me and 5 OAc. A pair of doublets centered at 3.90 ppm (J = 10.9 Hz) is created by the methylenic protons of a 17β-CH_2OAc group [20, 21]. Two doublets at δ 3.83 and 3.58 ppm (J = 9.6 Hz) indicate a transdiequatorial substitution of the C_{21} and D_{22} by two -OR groups (R = alkyl or H) [30]. One of these substituents would be an OH (IR absorption at 3460 cm^{-1}). A is a prosapogenin. The NMR spectra confirm this. On the mass spectrum of A, a $C_{18}H_{25}O_7$ ion corresponds to the base peak, an unusual composition for a fragment of triterpene, considering the known data in the literature. This peculiarity leads us to propose that the mass ion 353 accounts for the lateral chain of A.

The high number of ^{13}C NMR signals of A between 60 and 105 ppm suggests the presence of a sugar in this lateral chain [31]. The resonance observed at δ 102.3 ppm is due to the anomeric carbon [32]. Spin decoupling at 270 MHz enables the measurement of the coupling constants, J_{AX}, J_{AM}, J_{MX}, J_{AN}, J_{AV}, J_{NV}, J_{XA} (see Table 1). The chemical shifts and the values of the coupling constants observed for A, M, X, N, Y indicate that these protons are part of a highly substituted ring of the 6-deoxyhexose type [33]. The values of $J_{[illegible]}$ are compatible with the structure of a ring in which all the hydrogens are axial [33]. The protons A, M, X,N, Y and $A^1{}_3$ correspond respectively to the hydrogens 3'-H, 4'H, 5'-H, 2'-H, 1'-H and 6'-H (see **8-10**). This structure is that of the 6-deoxy-β-glucopyranose that is also called β-quinovose.

The δ of the protons of the quinovose ring indicate that the 1'-H proton is bonded to a carbon atom that is a carrier of an -OR group (R being different from a group with strong anisotropy such as Ac) and that the 2'-H, 3'-H and 4'-H protons are adjacent to the $-O_2CR$ groups [30]. The ^1H NMR study of the paramagnetic shifts induced by $Eu(DPM)_3$ [19] has revealed the presence of 5OAc in A. The existence of 4OAc on the triterpene part has been established by ^1H NMR. These results indicate that the quinovose is substituted by 3 acid molecules at the 2', 3' and 4' carbons. One of these substituents is an OAc.

In the carbon-13 NMR, A presents, in the domain of absorption of olefinic carbons, 6 signals which establish the existence of 6 sp^2 carbons (δ 124.9, 126.9, 127.0, 139.0, 139.4, 140.0 ppm). The absorptions observed on the out-of-resonance spectrum at δ 124.9 (d) and 140.0 ppm (s) are specific of the C_{12} and C_{13} of compounds of the Δ^{12} oleanene series [15, 28]. On this out-of-resonance spectrum, we also observe two signals corresponding to 2 quaternary olefinic carbons δ 126.9 (s) , 127.0 ppm (s) located at a higher field than the two absorptions attributed to 2 sp^2 carbons that are carriers of a hydrogen atom δ 139.0 (d) 139.4 (d). The position of these 4 signals demonstrates the presence of 2 unsaturated α-β carbonylated angles [34].

The catalytic hydrogenation of A gives a product H, which crystallizes from MeOH. The ^{13}C NMR of H (12) shows that of the 3 double bonds present in A, only the Δ^{12} remains in this compound. On the ^1H NMR spectrum of H, the disappearance of the multiplet signal observed on the spectrum of A at δ 6.04 ppm (2H = protons A^2 and $A^{2'}$)*. This establishes the olefinic nature of protons A^2 and $A^{2'}$ of the substance A.

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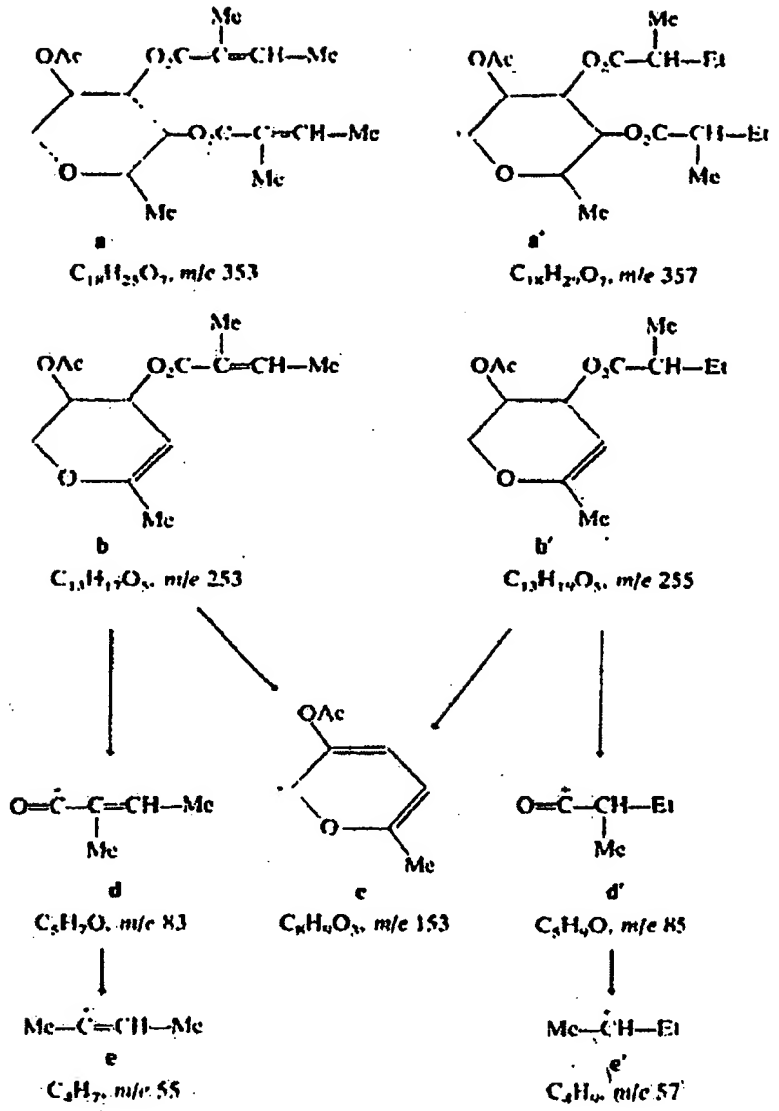
* Protons A^2 and $A^{2'}$ correspond to olefinic protons 9'-H and 9''-H of the lateral chain of A (see 8-10).



Schema 1. Fragmentation of the base peak observed in the MS of A (8), B (9), C (10) and H (12)

/619

In spectra recorded at 90 and 100 MHz, the signal due to protons A^2 and $A^{2'}$ is quite comparable to that caused by the protons of an AB system. At 270 MHz, this signal appears to result from the superposition of a pair of quadruplets. The protons A^2 and $A^{2'}$ are not coupled to each other. The spin decoupling at 270 MHz reveals that each of the protons is coupled at the same time with protons of an Me group (δ 1.95 ppm $^3J_{8/A2} = {}^{[illegible]}J_{X/A} = 6.8$ Hz) and a long way from protons of another Me group

(δ 1.83 ppm ($^4J_{v/A2} = {}^4J_{v/A2} = 1.4$ Hz). The group forming two systems with 7 spins $AX_{[illegible]}Y_{[illegible]}$, $A'X'_3Y'_3$.

According to the NMR results (^1H and ^{13}C), 2 molecules from the same acid are fixed to the quinovose. The structure of the anion corresponding to this acid is: cis-Me-CH=C(Me)=COO. Indeed, the value of the δ observed in NMR for the olefinic protons A^2 and $A^{2'}$ enables identifying this structure with that of the angelate ion rather than with that of the tiglate ion [35].

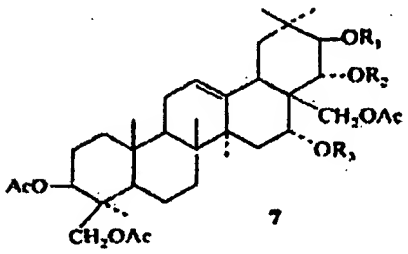
The result of this NMR data is that the lateral chain is formed by β-quinovose substituted at $C_{[illegible]}$ by an -OR group (R being the triterpene part of A) and at $C_{[illegible]}$, $C_{[illegible]}$, $C_{4'}$ by a molecule of acetic acid and two molecules of angelic acid.

The MS of A and its hydrogenation product H confirm the characteristics of the lateral chain. The fragments observed in the MS of A at 353, 253, 153, 83, 55 MU and those that appear for H at 357, 255, 253, 85, 57 MU correspond, respectively, to ions **a, b, c, d, e,** and **a', b', c, d', e'** (Schema 1).

All this spectral data leads to proposing for product A, one of the following six hypotheses of formulas with the following structures: **7a** (3 formulas) and **7b** (3 formulas), all likely to create ions **a, b, c, d, e** by fragmentation. The compared analysis of ^1H and ^{13}C NMR of A and B and C reveals that the lateral chains of these 3 products are identical. The presence in the MS of B and C of fragments with masses 353, 253, 153, 83 and 55 confirms it.

The triterpene part of B (**9**) is differentiated from protoaescigenin (**5**) at rings D and E. In the ^1H /620
NMR spectrum of B, absorption at δ 5.39 ppm (1H, t) due to the 16-H proton and a signal at δ 1.28 ppm (3H, s) attributable to the protons of Me_{27} indicate an α substitution of the C_{16} by an OAc [26]. A pair of doublets at δ 3.74 and 5.21 ppm (J = 10 Hz) due to protons 21α-H and 22β-H indicates a transdiequatorial substitution of carbons 21 and 22 by an OAc and an -OR group (R = alkyl or H) [30].

These δ, compared with those observed for protons 21α-H and 22β-H in F (5), indicate that the substituent -OR is carried by the C_{21}.



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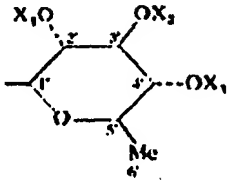


S

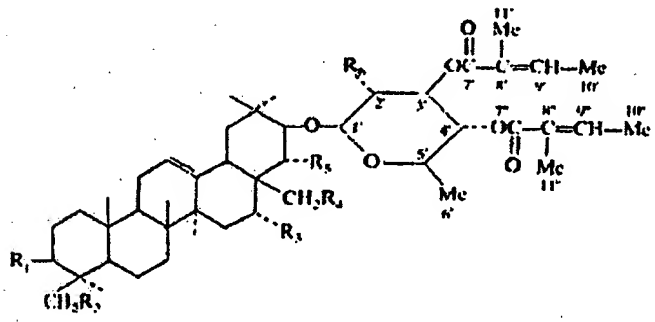
	R_1	R_2	R_3
7a	S	H	Ac
7b	S	Ac	Ac
7c	S	Ac	H
7d	H	S	Ac

$X_1, X_2, X_3 =$ { - Ac; - Angeloyl; - Angeloyl

Apart from signals due to the protons of the lateral chain, the ^1H NMR spectrum of C is distinguished from that of the protoaescigenin pentaacetate (F = 5) by the absorption due to the proton 21α-H. This proton resonates at δ 5.56 ppm (d) in F and at δ 3.84 ppm (d) in C. This proves the presence of a substituent -OR (R = alkyl or H) on the C_{21} in compound C.

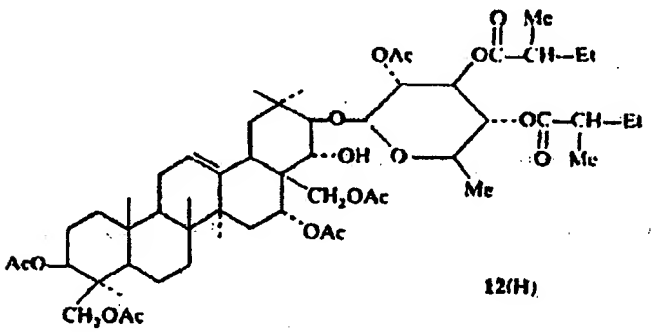
The NMR data fix the substitution of the triterpene part of A, B and C by the lateral chain on the C_{21}. The signals observed at δ 3.83 and 3.58 ppm in the spectrum of A are attributable, respectively, to protons 21α-H and 22β-H. In this compound, the C_{22} is substituted by an OH. The nonequivalence of the methylenic protons of the C_{28} presented by the ^1H NMR spectrum of A indicates the presence on C_{22} of this molecule with a different substituent than that carried by the same carbon in substance B. The greater deblinding (+ ~ 5 ppm) of the $C_{2[illegible]}$ observed in ^{13}C NMR in the case of product A ($\delta_{c[illegible]}$ 91.2 (A); 86.3 (B); 86.4 (C)) indicates the existence of an OH function in C_{22} [34].

All of these spectral characteristics lead us to propose for A, B, C, respectively, the structures **7a, 7b, 7c,** each likely to create 3 different formulas: the positions of the substituents on carbons 2', 3' 4' of the quinovose could not be differentiated by the analysis methods used. The study of compound B in the crystalline state by X-ray diffraction [36] has shown that the substituents of these carbons are found in the following positions: $C_{2'}$: OAc; $C_{[illegible]}$: angelate; $C_{3'}$: angelate.



		R_1	R_2	R_3	R_4	R_5	R_6
8	(A)	OAc	OAc	OAc	OAc	OH	OAc
9	(B)	OAc	OAc	OAc	OAc	OAc	OAc
10	(C)	OAc	OAc	OH	OAc	OAc	OAc
11	(D)	OH	OH	OH	OH	OH	OH

Thus, A, B, C have structures **8, 9, 10,** respectively. A, B, C derive from the same prosapogenin (**11**): 21β-[6-deoxy-3,4 diangelate-β-glucopyranosyl)oxy-3β,16α,22α,24,28-pentahydroxyolean-12-ene, for which we propose the name of napoleogenin. It is the first time that quinovose has been found as a component of prosapogenin [37] and that the fixation of a carbohydrate chain on carbon-21 of a genin derived from Δ^{12} oleanene has been encountered. The esterification of OH groups of a constitutive monosaccharide of a prosapogenin by angelic acid is also new. /621



12(H)

EXPERIMENTAL PART

Extraction of the saponin.

250 g of ground seeds of *Napoleonaea imperialis* are extracted at reflux for 3 h with 2.5 L of 80% MeOH. The extract is brought to dryness under reduced pressure. The residue is dissolved in MeOH, and then filtered on a Buchner. The addition of a quintuple volume of Et_2O to the filtrate precipitates the saponin, which is separated by filtration, then dried. Saponin is redissolved in MeOH to be again precipitated by Et_2O. The operation is repeated until a colorless powder is obtained. 250 g of seeds gave 14 g of saponin.

Hydrolysis and isolation of substances A (8), B (9), C (10), E (4), F (5). 3 g of saponin dissolved in 100 mL of an aqueous solution of 3.5% $HClO_4$ are placed in the oven in a sealed tube at 135° for 2 h. The hydrolysis precipitate is separated by filtration and washed with plenty of H_2O, then dried. The residue (900 mg) is acetylated with 30 mL of an Ac_2O-Py (1:1) mixture for 70 h at room temperature. The acetylated crude prosapogenin (1200 mg) is subjected to high-pressure liquid phase chromatography (HPLC column: RSIL 10 U silica; eluent: cyclohexane-EtOAc, 3: 1). Three products were isolated: A, 70 mg of crystals in the form of needles (MeOH) $C_{56}H_{82}O_{17}$ (found: C, 65.05; H, 8.2; O, 26.76; calculated: C, 65.49; H, 7.99; O, 26.51): B, 50 mg of crystals in the form of needles (MeOH) $C_{[illegible]}H_{84}O_{18}$ (found: C, 65.02; H, 8.27; O, 26.71; calculated: C, 65.16; H, 7.86; O, 26.96); C, 100 mg

noncrystalline $C_{[illegible]}H_{82}O_{17}$ (found: C, 65.46; H, 7.72; O, 26.82; calculated: C, 65.49, H, 7.99; O, 26.51).

Acid hydrolysis of the crude prosapogenin was continued in hydroalcoholic medium for 5 h ($HCl_{[illegible]}$ -H_2O-EtOH, 1:1:3). After evaporation of the alcohol, the hydrolysis precipitate is separated by filtration, and then dried under vacuum. The acetylation carried out as above has been followed by column chromatography with Woelm silica gel for dry column eluting: C_6H_6-EtOAc, 8:1). Two substances were isolated in the pure state: E, 25 mg, polygonal plates (MeOH) $C_{[illegible]}H_{58}O_9$ (found: C, 70.19; H, 8.45; O, 21.36; calculated: C, 69.30; H, 8.81; O, 21.89); F, 70 mg, noncrystalline, $C_{40}H_{60}O_{[illegible]}$ (found: C, 66.6; H, 8.92; O, 24.48: calculated: C, 67.03; H, 8.38; O, 24.58).

Identification of the sugars. The aqueous solution from perchloric hydrolysis is neutralized with KOH then brought to dryness. Anhydrous PY, which selectively dissolves the sugars, is added to the residue. The pyridine solution is then subjected to chromatographic analysis. The sugars have been identified by paper chromatography on Whatman No. 1 paper by the descending technique in the presence of controls. The mobile phase is formed of a mixture of n-BuOH-Py-H_2O, 6:4:3. Revelation carried out by spraying with aniline phthalate showed the presence of glucose and arabinose.

Catalytic hydrogenation of A (8) → H (12). 30 mg of A dissolved in 3 mL of EtOAc are hydrogenated in the presence of 5% palladiated carbon for 16 h at 120°. The catalyst is then filtered. Evaporation of the solvent leads to obtaining a residue that crystallized from MeOH: H (12) 26 mg (needles) $C_{[illegible]}H_{86}O_{17}$, MP = 221-223 °; $[\alpha]_D$ 12.1 ° ($CHCl_3$, c 0.1); λ^{MeOH}_{max} nm (log ε): 198 (3.98); MS m/e 657 (0.5%); 598 (3.8); 537(6.6); 519 (4.5); 477 (5); 417 (5); 357 (100); 307 (4.5); 255 (50); 228 (32); 215 (23); 195 (39); 153 (98); 85 (98); 83 (98); 57 (95); NMR δ (5.35) (2H) 12-H, 16β-H; 4.58 (part X of ABX, $(J_{AX} + J_{BX}) = 15.5$) 3α-H; 4.36; 4.12 (d, d, J = 11.5) 4β-CH_2OAc; 3.96, 3.84 (d,d,J = 10.3) 17β-CH_2OAc; 3.82, 3.56 (d,d, J = 9.2) 21α-H, 22β-H; 1.26-0.85 Me groups: 2.05 (6H, s), 2.06 (6H, s),

2.07 (3H, s) 5 OAc: 5.27 (3 peaks ($J_{AM} + J_{AN}$) = 18.9) 3'-H; 5.08 (3 peaks ($J_{AN} + J_{NM}$) = 17.8) 2'-H; 4.88 (3 peaks, ($J_{AM} + J_{MX}$) = 18.9) 4'=H; 3.60 (m, $J_{XA[illegible]}$ = 6.2) 5'-H; 1.23 (3H, d, $J_{A/N}$ = 6.2) 5'-Me; 4.48 (d, J_{YN} = 8.0) l'-H.

NMR. The ^{1}H NMR spectra were recorded for A, C and H on a Bruker 270 MHz spectrometer and for B on a Varian 300 MHz apparatus. The spectra of E and F, likewise, all the spectra listed in the presence of $Eu(DPM)_3$ were recorded on a Varian HA 100 spectrometer. The solvent used is $CDCl_3$ containing TMS as internal reference.

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Doc Code: TRAN.LET

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Evidence Appendix (E)(i)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	09/428,203
Filing Date	October 27, 1999
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Art Unit	1655
Examiner Name	Flood
Attorney Docket Number	WRAIR 98-36

ENCLOSURES *(Check all that apply)*

- [✓] Fee Transmittal Form
  - [ ] Fee Attached
- [✓] Amendment/Reply
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- [✓] Extension of Time Request
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- [ ] Drawing(s)
- [ ] Licensing-related Papers
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- [ ] Petition to Convert to a Provisional Application
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- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
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Date	16 March 2010	Reg. No.	36,681

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) **FY 2009** *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional)
Application Number 09/428,203	Filed October 27, 1999
For PLANT-DERIVED ANTI-PARASITIC AND ANTIFUNGAL COMPOUNDS AND METHODS OF . . .	
Art Unit 1655	Examiner Flood

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☑ One month (37 CFR 1.17(a)(1))	$130	$65	$ 130.00
☐ Two months (37 CFR 1.17(a)(2))	$490	$245	$
☐ Three months (37 CFR 1.17(a)(3))	$1110	$555	$
☐ Four months (37 CFR 1.17(a)(4))	$1730	$865	$
☐ Five months (37 CFR 1.17(a)(5))	$2350	$1175	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 210380.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 36,681

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

Signature — 16 March 2010 (Date)

Ms. Abanti Bhattacharyya, Esq. (Typed or printed name) — (410) 964-9553 (Telephone Number)

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☑ Total of 1 forms are submitted.

PTO/SB/17 (10-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 130.00

Complete if Known	
Application Number	09/428,203
Filing Date	October 27, 1999
First Named Inventor	Okunji
Examiner Name	Flood
Art Unit	1655
Attorney Docket No.	

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 210380 Deposit Account Name: USAMRMC

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims _____ - 20 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims _____ - 3 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims: Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets _____ - 100 = _____ Extra Sheets / 50 = _____ Number of each additional 50 or fraction thereof (round up to a whole number) x Fee ($) _____ = Fee Paid ($) _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): One Month Extension Of Time (Large Entity)	130.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 36,681	Telephone (410) 964-9553
Name (Print/Type)	Ms. Abanti Bhattacharyya, Esq.		Date 16 March 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner: Michele C. Flood
Christopher O. Okunji, et al.	Group Art Unit: 1655
Serial No.: 09/428,203	
Filing Date: October 27, 1999	
For: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS OF EXTRACTING THE COMPOUNDS	

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

REPLY UNDER 37 CFR §1.111

Dear Sir,

The following is a response under 37 CFR §1.111 to the Examiner's Office Action reopening prosecution subsequent to Applicants' filing of an appeal brief on May 22, 2009 and response to a non-compliant appeal brief filed July 21, 2009. Please note that the date of filing of the appeal brief stated in the Examiner's Office Action is incorrect.

This response in being filed within the one month extension period set to expire on March 16, 2010. A petition for an extension of time, a fee transmittal form and a transmittal form are attached herewith.

The Commissioner is hereby authorized to charge any fees that may be required in connection with the filing of this request, as well as credit any overpayment, to US Army Medical Research and Materiel Command, Deposit Account Number 210380.

Additionally applicants respectfully request that the appeal fee paid in the filing of the appeal be credited to the deposit account above.

(1) A marked copy of the claims begins on page 3.

(2) A clean copy of the claims begin on page 4.

(3) Remarks begin on page 6.

MARKED COPY OF THE CLAIMS

Claim 1 (previously presented). A biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

Claims 2-10 are cancelled.

Claim 11 (previously presented). A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoloenaea imperialis* utilizing said solvent.

Claims 12-29 are cancelled.

Claim 30 (currently amended). A biologically active extract according to claim 1, wherein said solvent is methanol, and wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

Claims 31- 37 are cancelled.

Claim 38 (previously presented) A biologically active extract according to claim 11, wherein said solvent is methanol.

Claims 39 and 40 are cancelled.

CLEAN COPY OF THE CLAIMS

Claim 1 (previously presented). A biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

Claims 2-10 are cancelled.

Claim 11 (previously presented). A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoloenaea imperialis* utilizing said solvent.

Claims 12-29 are cancelled.

Claim 30 (currently amended). A biologically active extract according to claim 1, wherein said solvent is methanol, and wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

Claims 31- 37 are cancelled.

Claim 38 (previously presented) A biologically active extract according to claim 11, wherein said solvent is methanol.

Claims 39 and 40 are cancelled.

REMARKS

1. The Examiner has objected to claim 30 for an informality. The word "and" was missing from the claim recitation. Correction to the claim has been made. The addition of the word does not add new matter or change the meaning or scope of the recitation of the claim as previously presented.

2. In view of the Appeal Brief filed by Applicants on July 24, 2009, the Examiner has reopened prosecution on this application and hereby entered claims 1, 11, 30 and 38. Thereafter, the Examiner has newly rejected claims 1, 11, 30 and 38 as being anticipated by Kapundu et al under 35 USC §102(b). In response to the newly applied rejection, Applicants are given the statutory option of filing a new notice of Appeal or to respond to the Office Action under 37 CFR §1.111. In their duty to further prosecution on its merits, Applicants hereby reply to the Office Action under 37 CFR §1.111.

We begin by presenting the relevant portions of the prosecution history of this application to date and follow with rebuttal arguments to the Examiner's rejection.

(a) The Kapundu et al reference was first raised by the Examiner in her Office Action of October 25, 2002 to the parent application. It was then raised in the RCE non-final Office Action of May 30, 2007. However, in the subsequent Office Action of March 28, 2008, the prior art rejection of the claims are based on another reference and Kapundu et al is not mentioned. In subsequent communications with the Examiner, namely a telephonic interview, Applicants' proposed amendments would likely place the application in condition for allowance. The Examiner notes that the only condition against allowance would be the discovery of prior art that reads on the claimed invention.

See Interview Summary Record of July 24, 2008. However, the Examiner issues an Advisory Action on August 21, 2008 stating that the amendment was not entered because "Applicant's insertion of the limitation "fractionated" would require further search and/or consideration122". *See* Note 3, of the Advisory Action, August 21, 2008. Applicants filed an Appeal Brief on May 22, 2009 on several grounds including the fact that the term "fractionated" was suggested by the Examiner in the Office Action of March 28, 2008 which initiated the telephonic interview and the Applicants' reliance on the Examiner's explicit statements made in the Interview Summary Record. Kapundu et al is not mentioned in any of these communications.

Applicants respectfully traverse the Examiner's rejection and contend that the present Office Action is outside the scope of examination practices. While reopening of prosecution provides the Examiner a procedural mechanism to enter the claims, newly rejecting them on Kapundu et al. is questionable as the amendments to the claims were addressed by the Examiner in the Telephonic Interview and the subsequent Advisory Action, neither of which mention the Kapundu et al reference. Furthermore, Applicants note that the Examiner presents the same inherency arguments (see rebuttal arguments below) that she had presented in her Office Actions prior to March 28, 2008 and ceased to continue thereafter. Such practices do not further prosecution and fail to provide Applicants the full and bona fide examination practices to which they are entitled.

Additionally, please note that the current Office Action makes no mention of the prior art rejection of the March 28, 2008 rejection. Based on the prosecution history, it is the Applicants strong position that the omission of Kapundu et al reference in the March 28, 2008 Office Action and the omission of the Okunji et al reference in the November

16, 2009 Office Action are explicit showings that both references have been overcome. This is the standard and accepted prosecution practice before the USPTO. Thus, it is the Applicants' position that the claims are now in condition for allowance.

(b) The present rejection now states that the previously presented Kapundu et al reference which discloses hydrolyzed methanolic powdered seed extract of *Napoloneae imperialis* anticipates these claims as "the claim-designated plant comprises saponin....the claim-designated functional effect is considered inherent to the extract taught by Kapundu, because the source of the plant, the particular plant material from the source plant and the solvent used in the making of the plant extract taught by Kapundu are one and the same as disclosed by Applicant." See Examiner's Office Action of November 16, 2009 at 4.

Applicants respectfully traverses the rejection. In order to invoke the standard of inherency there must be a basis in fact and/or technical reasoning to reasonably support that the allegedly inherent characteristic flows from the teachings of the prior art. *See* MPEP §2112. Applicants have consistently maintained that the Examiner has failed to meet her burden under this standard. For example, Applicants' 132 affidavit discusses and distinguishes Kapundu et al in detail. Specifically, the point that Kapundu et al is strictly dependant upon the hydrolyzed seed extracts of *N. imperialis*. and the particular reasons why saponin hydrolyzation is counterintuitive and consequently counterproductive to the novel and unobvious characteristics of the present invention. To note: "the saponins were first hydrolyzed before isolation and chemical identification of the constituents...The product of hydrolysis is simpler, yielding low molecular weight

compounds, less polar, less complex structurally and easy to handle... In contrast [sic] ....only naturally occurring pharmacologically active compounds were pursued...rather than hydrolyzed products....present knowledge on *N. imperialis* indicated that the major constituents of this plant are the saponins....saponin contents have been reported to vary depending on factors (discussing geographic location)...saponin distribution among the organs of a plant may vary considerably (citing as example the variation in saponin concentration in marigold flowers varies significantly from that of the roots)....Our work on Dracaena species revealed that vary high saponin content are found mostly in the seeds." *See* Applicant's §132 affidavit at 6. Note also that Applicants specifically discuss the problems associated with hydrolysis of saponins as taught by Kapundu et al. These include complications with artifact formation, low yields, low selectivity and difficulty with structure elucidation. *See* id at 8. These factual distinctions have been repeatedly raised in rebuttal arguments by Applicants during prosecution. However, the Examiner has not addressed these distinctions in her rebuttal arguments. Instead the Examiner has continued to provide factually unsupported conclusions such as those identified above. Such a rejection is without merit and continues to fail to meet the required burden of the inherency standard. Without the substantive factual basis required to meet the burden of inherency the Examiner cannot sustain any prior art inherency standard rejection. Therefore, Applicants respectfully submit that the prior art rejection is overcome for the reasons stated in (a) and (b) above. Therefore, Applicants respectfully solicit that the present claims be placed in condition for allowance.

Please send all correspondences to: Elizabeth Arwine, Esq., Office of the Staff Judge Advocate, US Army Medical Research and materiel command; 504 Scott Street,

Fort Detrick, MD 21702-5012: Attn: MCMR-JA (Ms. Arwine). Please direct any questions regarding this case to Ms. Abby Bhattacharyya, Esq. at (410)964-9553.

Sincerely,

16 March 2010
Date

A. Bhattacharyya, Esq.
Reg. No. 36,681

EVIDENCE APPENDIX (E)(i)

PTO/SB/21 (01-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	09/428,203
Filing Date	October 27, 1999
First Named Inventor	Okunji, Christopher O.
Art Unit	1655
Examiner Name	Flood, Michele C.
Attorney Docket Number	003/172/SAP

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
- [x] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [x] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please identify below):

Remarks

Petition for an extention of time
Fee Transmittal Form
Return Receipt Postcard

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Bartunek & Bhattacharyya, Ltd.		
Signature			
Printed name	Abanti A. Bhattacharyya, Esq.		
Date	July 24, 2008	Reg. No.	36,681

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name	Abanti A. Bhattacharyya, Esq.	Date	July 24, 2008

COPY

PTO/SB/22 (01-08)
Approved for use through 07/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2008 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 003/172/SAP
Application Number 09/428,203	Filed October 27, 1999
For Plant Derived Anti-Parasitic And Antifungal Compounds and Methods For Extracting the Compounds	
Art Unit 1655	Examiner M. Flood

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☑ One month (37 CFR 1.17(a)(1))	$120	$60	$ 120.00
☐ Two months (37 CFR 1.17(a)(2))	$460	$230	$
☐ Three months (37 CFR 1.17(a)(3))	$1050	$525	$
☐ Four months (37 CFR 1.17(a)(4))	$1640	$820	$
☐ Five months (37 CFR 1.17(a)(5))	$2230	$1115	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 210380. I have enclosed a duplicate copy of this sheet.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

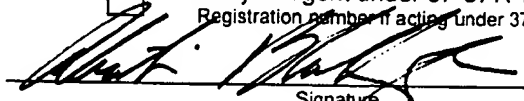
I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☑ attorney or agent of record. Registration Number 36,681

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____


Signature

July 24, 2008
Date

Abanti A. Bhattacharyya
Typed or printed name

(910)964-9553
Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

COPY

PTO/SB/17 (10-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act. 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2008

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($)

Complete if Known	
Application Number	09/428,203
Filing Date	October 27, 1999
First Named Inventor	Okunji, Christopher O.
Examiner Name	Flood, Michele C.
Art Unit	1655
Attorney Docket No.	003/172/SAP

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 210380 Deposit Account Name: USAMRMC

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fees Paid ($)
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	210	105
Multiple dependent claims	370	185

Total Claims _____ - 20 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims _____ - 3 or HP = _____ Extra Claims x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims: Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets _____ - 100 = _____ Extra Sheets / 50 = _____ Number of each additional 50 or fraction thereof (round up to a whole number) x Fee ($) _____ = Fee Paid ($) _____

4. OTHER FEE(S)

Fees Paid ($)

Non-English Specification, $130 fee (no small entity discount) _____

Other (e.g., late filing surcharge): 1 mo extension of time, after-final amendment $930.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 36,681	Telephone (410)964-9553
Name (Print/Type)	Abanti A. Bhattacharyya, Esq.		Date July 24, 2008

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

COPY

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF

APPLICANT:	Okunji et al.	DATE:	July 24, 2008
SERIAL NO.:	09/428,203	GROUP ART UNIT:	1655
FILED:	October 27, 1999	EXAMINER:	M. Flood

FOR: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS FOR EXTRACTING THE COMPOUNDS

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

The following is an after-final response to the Examiner's office action of March 28, 2008. Applicants respectfully request that the response be entered. Applicants also respectfully request a one month extension of time set to expire on July 28, 2008. A petition for an extension of time, a fee transmittal form and a transmittal form are attached hereby. The Commissioner is hereby authorized to charge any fees that may be required in connection with the filing of this request, as well as credit any overpayment, to U.S. Army Medical Research and Materiel Command, Deposit Account Number 210380.

(1) A marked copy of the claims, with amendments, begins on page 3.

(2) A clean copy of the claims, with amendments, begins on page 5.

(3) Remarks begin on page 7.

Marked Copy of the Claims:

1. (currently amended) A biologically active extract comprising a fractionated ~~fractionation~~ extract from ~~at least one plant selected from the group consisting of *Aframomum aulocacarpus*, *Aframomum danielli*, *Dracaena arborea*, *Eupatorium odoratum*, *Glossocalyx brevipes* and~~ *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

2 through 10 (cancelled)

11. (previously presented) A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

12 through 29 (cancelled)

30. (currently amended) A biologically active extract according to claim 1, wherein said solvent is ~~selected from a group consisting of hexane, chloroform, ethyl acetate and~~

methanol, wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

31 through 37 (cancelled).

38. (previously presented) A biologically active extract according to claim 11, wherein said solvent is methanol.

39 through 40 (cancelled).

A Clean Copy of the Claims:

1. (currently amended) A biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

2 through 10 (cancelled)

11. (previously presented) A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

12 through 29 (cancelled)

30. (currently amended) A biologically active extract according to claim 1, wherein said solvent is methanol, wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

31 through 37 (cancelled).

38. (previously presented) A biologically active extract according to claim 11, wherein said solvent is methanol.

39 through 40 (cancelled).

Remarks:

(1) Applicants wish to thank Examiner Flood for the telephonic interview of July 24, 2008. Applicants respectfully request that this after-final amendment be entered as it places the present application in condition for allowance for the reasons given below.

(2) The Examiner states that "The elected species, namely *Napoleonaea imperialis*, the solvent methanol and the seed portion of the plant, was not found." See Examiner's Action of March 28, 2008, page 2.

Applicants have amended claims 1, 11 and 30 to only recite the species *Napoleonaea imperialis*, the seed extracts of the species and the organic solvent, methanol. Applicants have cancelled pending claims 2 through 10, 12 through 29, 31 through 37 and 39 through 40 to better recite the invention of the present applications. Applicants, however, reserve their rights to file a divisional application directed to all of the cancelled claims. Based on the Examiner's acknowledgment and telephonic interview, it is the Applicants' position that the amendments to claims 1, 11 and 30 place pending claims 1, 11, 30 and 38 in condition for allowance.

(3) Applicants acknowledge the Examiner's rejection of claims 1, 11, 12, 30, 31 and 38 under 35 USC 112 2nd paragraph. Applicants have amended claim 1 to better recite the invention and overcome the rejection of the claims. Applicants discussed the claim amendments in the telephonic interview with the Examiner of record. Based on the Examiner's action and the telephonic interview, it is the Applicants' position that the amendment to claim 1 overcomes the 112 2nd paragraph rejection and places the claims in condition for allowance.

(4) Applicants acknowledge the Examiner's rejection of claims 1, 12, 30 and 31 under 35 USC 102(b) as being anticipated by Okunji, et al.

Based on the amendments to the claims above, the Examiner's acknowledgement discussed in (1) above and the telephonic interview, the rejection of the claims is moot and a discussion by Applicants of the Examiner's rejection is no longer relevant.

Early allowance of claims 1, 11, 30 and 38 is respectfully solicited.

The Examiner is respectfully requested to send all correspondences to: Elizabeth Arwine, Esq.; Office of the Staff Judge Advocate; U.S. Army Medical Research & Materiel Command;

504 Scott Street, Fort Detrick, Maryland 21702-5012; Attn: MCMR-JA (Ms. Arwine).

Please direct any questions regarding this case to Ms. Abby Bhattacharyya, Esq. at (410) 964-9553.

July 24, 2010
Date

Abanti A. Bhattacharyya, Esq.
Reg. No. 36,681

Doc Code: TRAN.LET

Document Description: Transmittal Letter

EVIDENCE APPENDIX(E)(i)

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Total Number of Pages in This Submission: 137

Application Number	09/428,203
Filing Date	October 27, 1999
First Named Inventor	Christopher O. Okunji
Art Unit	1655
Examiner Name	Michele C. Flood
Attorney Docket Number	MEMC.PA.01.02

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
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- [ ] Appeal Communication to Board of Appeals and Interferences
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- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Bartunek & Bhattacharyya, Ltd		
Signature			
Printed name	Abanti A. Bhattacharyya, Esq.		
Date	May 22, 2009	Reg. No.	36,681

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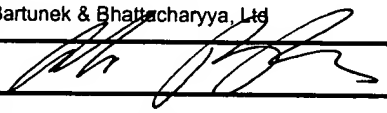
Signature			
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Date	May 22, 2009	Reg. No.	36,681

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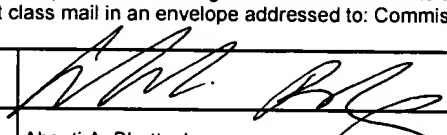
Signature			
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FEE TRANSMITTAL
For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($)	540.00

Complete if Known	
Application Number	09/428,203
Filing Date	October 27, 1999
First Named Inventor	Christopher O. Okunji
Examiner Name	Michele C. Flood
Art Unit	1655
Attorney Docket No.	MRMC.PA.01.02

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 210380 Deposit Account Name: USAMRMC

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims _____ - 20 or HP = _____ x _____ = _____ Extra Claims / Fee ($) / Fee Paid ($)

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims _____ - 3 or HP = _____ x _____ = _____ Extra Claims / Fee ($) / Fee Paid ($)

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets _____ - 100 = _____ Extra Sheets / 50 = _____ Number of each additional 50 or fraction thereof (round up to a whole number) x _____ Fee ($) = _____ Fee Paid ($)

4. OTHER FEE(S)

Non-English Specification, $130 fee (no small entity discount) Fees Paid ($) _____

Other (e.g., late filing surcharge): Filing of an Appeal Brief $540.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 36,681	Telephone (410)964-9553
Name (Print/Type)	Abanti A. Bhattacharyya, Esq.		Date May 22, 2009

PTO/SB/17 (10-08)
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Examiner Name	Michele C. Flood
Art Unit	1655
Attorney Docket No.	MRMC.PA.01.02

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 210380 Deposit Account Name: USAMRMC

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☑ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

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Other (e.g., late filing surcharge): Filing of an Appeal Brief $540.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 36,681	Telephone (410)964-9553
Name (Print/Type)	Abanti A. Bhattacharyya, Esq.		Date May 22, 2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner: Michele C. Flood
Christopher O. Okunji, et al.	Group Art Unit: 1655
Serial No.: 09/428,203	
Filing Date: October 27, 1999	
For: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS OF EXTRACTING THE COMPOUNDS	

APPEAL BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1451
Alexandria, VA 22313-1451

Dear Sir:

Applicants submit the following Appeal Brief. This brief is timely filed within the two month period of response that expires on May 24, 2009. The Commissioner is hereby authorized to charge any fees that are required, as well as any additional fees that may be required in connection with the filing of this paper, or credit any overpayment, to U.S. Army Medical Research and Materiel Command, Deposit Account Number 210380. Please send all correspondences to Ms. Elizabeth Arwine, Esq.; Office of the staff Judge Advocate; U.S. Army Medical Research and Materiel Command; 504 Scott Street; Fort Detrick, MD 21702-5012, Attn: MCMR-JA (Ms. Arwine). Please direct any questions regarding this case to Ms. Abanti (Abby) Bhattacharyya, Esq., at (410) 964-9553.

Sincerely,

Date

Abanti A Bhattacharyya, Esq.
Reg. No. 36,681

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Examiner: Michele C. Flood
	)	
Christopher O. Okunji, et al.	)	Group Art Unit: 1655
	)	
Serial No.: 09/428,203	)	
	)	
Filing Date: October 27, 1999	)	
	)	
For: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS OF EXTRACTING THE COMPOUNDS	)	

APPEAL BRIEF

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is U.S. Army Medical Research and Materiel Command of Fort Detrick, Maryland.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences that will affect or be affected by the outcome of this appeal.

III. STATUS OF THE CLAIMS

For the purposes of this Appeal, Applicants provide a status of the claims that conforms with the non-entered amendment of July 24, 2008. Thus, the present application recites claims 1 through 40. Claim 1 is currently pending in this application. Claims 2 through 10 are cancelled. Claim 11 is currently pending in this application. Claims 12 through 29 are cancelled. Claim 30 is currently pending in this application. Claims 31 through 37 are cancelled. Claim 38 is currently pending in this application. Claims 39 through 40 are cancelled.

IV. STATUS OF THE AMENDMENTS

An amendment and response was filed by Applicants on July 24, 2008, in response to the Examiner's final rejection of March 28, 2008. The amendment and response was not entered. For the purposes of this Appeal, Applicants respectfully request that only the claims of the non-entered amendment, claims 1, 11, 30 and 38, be considered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is directed to a saponin-enriched fractionated extract of *Napoleonaea imperialis* that exhibits aniti-leishmanial activity. The extract has been effective in treating *Leishmania* while having low-toxicity for humans. *See* Specification at 14. The recitation in claim 1 is based upon findings that traditional medicines may provide efficacy against protozoan infections without the side-effects encountered when utilizing conventional pharmaceuticals. Claim 11 is dependent upon claim 1 and recites direct solvent extraction of the powdered seeds of *Napoleonaea imperialis*. Direct solvent extraction of the powdered seeds was found to be the most effective technique to extract the saponin-enriched fraction recited in claim 1. *See id.* The extraction was conducted in three batches utilizing the solvents hexane, chloroform, ethyl acetate and methanol. The methanol extract was found to be the most active fraction and is recited in claim 30, which is dependant upon claim 1, and claim 38, which is dependant upon claim 11.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed in this appeal are as follows:

A. Are claims 1, 11, 30 and 38 unpatentable under 35 U.S.C. 112 2nd paragraph for failing to particularly point out and distinctly claim the subject matter by reciting "A biologically active extract comprising a fractionation extract." Additionally, is an acknowledgement of utility by the Examiner of the term under 35 U.S.C.§101 inconsistent with a finding of ambiguity of the same term under 35 U.S.C.§112 2nd paragraph.

B. Is the Examiner's denial of entry of Applicants Amendment and Response of November 30, 2007, outside the scope of examination practice under 37 C.F.R.§ 1.116(b) where Applicants have shown good and sufficient reasons for the amendments when:

(1) The Examiner's position that the grounds for non-entry of Applicants amendment is a prior art search necessitated by amendment, based on the Applicants claim recitation of "fractionated," where previous claims recited "fractionation;"

(2) Where the term "fractionated" was suggested by the Examiner in the Office Action to which the Applicants were responding; and

(3) Where in preparing the amendment and response, Applicants relied on the Examiner's Office Action and subsequent telephone interview record of July 24, 2008 stating "Applicant's representative, Abby Bhattacharyya, proposes limiting the species recited in Claim 1 to *Napoleonaea imperialis* and cancelling claims 2-10, 12-29, and 31-35. Amending the claims as discussed would appear to obviate the rejections of record and place Claims 1, 11, 30 and 38 in condition for allowance absent discovery of prior art that reads on the claimed subject matter."

C. Are claims 1, 11, 30 and 38 unpatentable under 35 U.S.C. 102(b) as being anticipated by Christopher O.Okunji et al., *Biological Activity of Saponins from Two Dracaena Species*, 404 Adv. Exper. Med. Bio. 415(1996).

VII. ARGUMENT

Errors of Law and Fact

1. The Examiner has made final her rejection of claims 1, 11, 30, and 38 under 35 U.S.C. §112 2nd paragraph for the recitation of " a biologically active extract comprising a fractionation extract" because "it is not clear as to the subject matter to which Applicant intends to seek patent protection. For example, plant material may be initially extracted with either water or methanol as a solvent in the making of a crude plant extract followed by subjecting the crude plant extract to fractionation with one or more solvents of increasing polarity or increasing strength." *See* Office Action, at 3 (Mar. 28, 2008).

It is established that the words of the claims, asserted and unasserted, define the scope of the patented invention. *See Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34 USPQ 2d 1816, 1819 (Fed. Cir. 1995). Despite the fact that claims are generally given their ordinary and customary meaning, patentee may choose terminology that is outside of the ordinary and customary meaning, provided that the chosen terminology is clearly defined in the Applicants' specification. *See Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578, 38 USPQ2d 1126, 1129 (Fed. Circ. 1996) (holding that a technical term in patent documents is considered as having the meaning given by persons experienced in the field of the intention unless it is clear from the patent and the prosecution history that the inventor used the term with a different meaning).

Applicants contend that they are consistent with established case law and provide adequate support in the specification for the claim recited term "biologically active extract." While the term "fractionation" may have a different meaning for persons experienced in the field, the applicants have adequately defined their meaning in the specification. Note that the Applicants

utilize "bulk extracts," "active extracts" and "fractions" interchangeably and provide substantive disclosure of the term and what is meant by it to preclude confusion by one of ordinary skill in the art. *See* Specification 10, 15, 17. Additionally, Applicants have provided an affidavit under 37 CFR §1.132 to distinguish between "hydrolyzed extracts" and "active extracts." *See* Response (132 Declaration) at 14 (Jun 4, 2004). Thus, it is the Applicants' position that the Examiner is factually and legally in error that Applicants' consistent recitation of "biologically active extract" is inadequately disclosed such that its meaning is ambiguous under 35 USC §112 2nd paragraph and that the recitation renders the claims as indefinite.

In conforming with examination practices under MPEP §2107.03, the Examiner acknowledges "that Applicant has demonstrated *in vitro* and/or *in vivo* antileishmanial, antifungal or antimalarial activities of compounds AD-1 obtained from a seed extract of *Napoleonaea imperialis*, using either ethyl acetate or methanol." See Office Action at 3 (Apr. 4, 2002). Inherent in the Examiner's statements that Applicants conform to the *in vitro* and *in vivo* antileishmanial activity of the seed extract of *Napoleonae imperialis* is an implicit understanding that the terminology utilized by the Applicants in the specification, the manner of its use in the specification and the conclusions reached by the Applicants is unambiguous. Without the implicit understanding, the Examiner cannot ascertain utility. Thus if the Examiner asserts that "biologically active extracts" and "fractionation" merits substantive clarity in the specification, she cannot then assert that these terms are ambiguous in the claims, for claims must be "given the broadest reasonable interpretation consistent with the specification." *See* MPEP§904.01, §2111 (Jul 2008).

2. As provided for in 37 C.F.R§116(b) an amendment after final rejection will be entered if "(1) canceling claims or complying with any requirement of form expressly set forth in

a previous Office Action; or (3) An amendment touching the merits of the application may be admitted upon a showing of good and sufficient reason why the amendment is necessary and was not earlier presented." See 37 C.F.R. §116(b) at 89 (Jul 2008).

As stated, the Applicants' after-final Amendment conformed to the substantive issues raised by the Examiner's Office Action. With respect to the Examiner's rejection of the claims under 35 U.S.C. 112 2nd paragraph, Applicants provided amendments to limit claim recitation to a fractionated seed extract of *Napoleonaea imperialis* and the solvent methanol. Please note that the term "fractionated" was suggested by the Examiner in her Office Action. To further confirm that these recitations were in line with the Examiner's position in the Office Action, Applicants' representative initiated a telephone interview that was made of record, the substance of which is stated above. In addition, the Examiner clearly states that the 35 U.S.C §102 (b) rejection of the claims is due to the Markush recitations. *See supra.* In conforming with after-final amendment practice and in reliance on the statements made by the Examiner in her Office Action and subsequent Interview Summary Record, Applicants strongly assert that they have met the relevant portions of 37 C.F.R §116(b) and that the Examiner erred in denying entry of the after-final Amendment and that entry of the after-final Amendment would have resulted in the allowance of the claims in dispute.

Furthermore, as stated in the MPEP, "The first search should be such that the examiner need not ordinarily make a second search of the prior art, unless necessitated by amendments to the claims by the applicant in the first reply, except to check to determine whether any reference which would appear to be substantially more pertinent than the prior art cited in the first Office action has become available subsequent to the initial prior art search. The first search should cover the invention as described and claimed, *including the inventive concepts toward which the*

claims appear to be directed. It should not be extended merely to add immaterial variants (emphasis added)." *See* MPEP§904 (Jul 2008). Applicants initially presented the claim recitation of "fractionation" in response to the Examiner's position that "non-hydrolyzed extract" lacked antecedent basis and constituted new matter. As the discussions of direct extraction versus hydrolyzed extraction became the focal point in distinguishing the present invention from that of the prior art, Applicants utilized the term "fractionation" in their claim recitation because its definition was adequately supported by the specification. *See* Examiner's Office Action at 4 (May 30, 2007); Applicants' Response at 10 (Nov. 30, 2007) and *supra*. Factually, the recitation was accepted by the Examiner as evidenced in her Office Action where she states "It would appear that Applicant intends to direct the subject matter of the claimed invention to a biologically active extract comprising a *fractionated* (emphasis added) extract from at least one plant selected from the claim-designated Markush group recited in Claim 1." *See* Examiner's Office Action at 2 (Mar 28, 2008). The statement by the Examiner provides direct evidence that "fractionating" was understood as defined by the Applicants specification, recited in the claims and supported by MPEP§904. This is further substantiated by the statement presented in the Interview Summary Record. *See supra*. Therefore, the Applicants assert that the Examiner's statements provides implicit evidence that the amendments to the claims changing "fractionating" to "fractionated" are inventive concepts towards which the claims are directed and are also immaterial varients that would not necessitate further searching. *See Supra*. Furthermore, Applicants' amendments to the claims were made in a good faith reliance of the statements in the Examiner's Office Action and in the Telephone Interview Summary Record stating that such amendments would result in an allowance of the claims. In addition to the MPEP *supra*, Applicants respectfully submit that the age of electronic searching substantially

dilutes the Examiner's position that a mere tense change of a word necessitates additional searching to the level that will deny entry of an amendment.

3. Applicants contend that claims 1, 11, 30 and 38 are not anticipated by Applicant's prior art since the Examiner acknowledges that "the elected species, namely *Napoleonaea imperialis*, the solvent methanol and the seed portion of the plant, was not found..." *See* Office Action 2, line3 (Mar 28, 2008) (holding that, as a Markush group, the claims are anticipated by Christopher O. Okunji et al., *supra*, due to Applicants recitation of *Dracaena arborea*). As stated above, Applicants are placing before the board the claims as recited in the submitted Office Action of July 24, 2008 that limit claim recitation to that acknowledged by the Examiner. See *supra*. This acknowledgement is of particular concern as Applicants have narrowed claim recitation in reliance on the Examiner's position.

In view of the body of evidence provided above, Applicants' continue to contend that the Examiner's position is without merit. Therefore, Applicants respectfully submit that the Board overturn the rejection of claims 1, 11, 30 and 38 and hold these claims allowable.

Sincerely,

May 22, 2009
Date

Abanti A. Bhattacharyya, Esq.
Reg. No. 36,681

VIII. CLAIMS APPENDIX

The claims involved in this Appeal are as follows:

1. A biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent, and wherein said biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity.

11. A biologically active extract according to claim 1, wherein said extract is obtained directly from solvent extraction of powdered seeds of *Napoleonaea imperialis* utilizing said solvent.

30. A biologically active extract according to claim 1, wherein said solvent is methanol, wherein said extract is obtained directly from solvent extraction of powdered seeds of said plant utilizing said solvent.

38. A biologically active extract according to claim 11, wherein said solvent is methanol.

IX. EVIDENCE APPENDIX

(A) Cited Case Law (in order of appearance in the appeal brief):

1. *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34USPQ 2d 1816, 1819 (Fed. Cir. 1995);

2. *Hoechst Celanese Corp. v BP Chems. Ltd.*, 78 F.3d 1575, 157, 38 USPQ 1126, 1129 (Fed. Circ. 1996).

(B) Manual of Patent Examination Procedure Sections(in order of appearance in the appeal brief):

1. MPEP§2107.03

2. MPEP§904.01;

3. MPEP§2111;

4. MPEP §904.

(C) Prior Art Citation:

Christopher O. Okunji et al., *Biological Activity of Saponins from Two Dracaena Species*, 404 Adv. Exper. Med. Bio. 415 (1996).

X. RELATED PROCEEDINGS APPENDIX

None

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Application Number	09/428,203
Filing Date	October 27, 1999
First Named Inventor	Okunji
Art Unit	1651
Examiner Name	Flood
Attorney Docket Number	MRMC.PA.01.12

Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- [✓] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [✓] Other Enclosure(s) (please Identify below):
  1. Petition to Revive

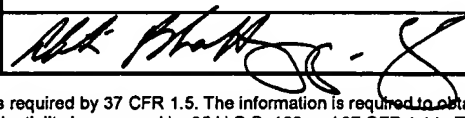
Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Abanti Bhattacharyya Singla, Esq. Bartunek & Bhattacharyya, Ltd.
Signature	
Date	June 4, 2004

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Abanti Bhattacharyya Singla, Esq.		
Signature		Date	June 4, 2004

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	)	
	)	
APPLICANT: Okunji, et al.	)	DATE:
	)	
SERIAL NO.: 09/428,203	)	GROUP ART UNIT: 1651
	)	
FILED: October 27, 1999	)	EXAMINER: M. Flood
	)	
FOR: PLANT DERIVED ANTI-PARASITIC AND ANTI-FUNGAL COMPOUNDS AND METHODS FOR EXTRACTING THE COMPOUNDS	)	

RULE 132 DECLARATION

1. I, Christopher O. Okunji, do hereby declare that:

2. I am a Ph.D. Pharmacognosist, Senior Research Associate at LTS Corporation, Bethesda, Maryland.

During the patent application process my employment as Senior PhD Research Pharmocognosist, was as follows:

Date	Patent Information activities	Employment (agency paid salary)
1990-1993	invention conceived	University of Nigeria, Nsukka
03-1993-1996	invention developed first drafted	National Science Foundation and International cooperative Biodiversity Grant (ICBG), USA
1996-	invention disclosed (provisional)	ICBG - fund from NIH
	invention submitted as PTO application	ICBG - fund from NIH
06-03-2005	invention prosecution	ICBG (left WRAIR)
06-04-2004 10-23-2005	"	self-employed
10-24-2005 04-28-2006	"	Rutgers University, Biotech Center, NJ
05-01-2006 – present	"	LTC Corporation (Fed contractor)

3. I wish to state that the references of record by researchers/scientists (Mbah, et al., and Ekpendu, et al.) were made known to me, and that my work as stated in the above-identified patent application is substantially different from the art of record. My work on *Napoleonaea* is part of my Ph.D. dissertation, specifically the use of seeds vs. that of other plant parts such as extracts. (see detail item 6). To illustrate the above points, my research interest on the genus *Napoleonaea* started as far back as 1983 when I screened this plant for molluscicidal activity. My Ph.D. dissertation in 1987, entitled "Molluscicidal and Antifungal Properties of Some Nigerian Medicinal Plants,"
http://www.unn-edu.net/postgrad/pg fac of pharm sci.htm
identified *Napoleonaea vogeli* auct. (Fam. Lecythidaceae; synonyms: *Napoleonaea imperialis* P. Beauv.) as potential plant molluscicides. Further screening of this plant for antileishmanial activity in 1993 identified *Napoleonaea imperialis* seeds as having a promising antileishmanial activity. Bioassay guided-chromatographic fractionation of *Napoleonaea imperialis* seeds yielded imperialisides (A-C).

4. That the work of Mbah, et al., was on the antibacterial activity of extracts from leaves, stem-bark, root and root-bark

of *Napoleonaea imperialis* without specific identification of any phytochemical constituent, while my work on the seed specifically identified three antileishmanial compounds belonging to the class saponin. Please note that the conclusion of the Mbah, et al., reference states: "...the absence of toxic affects for the flavonoids and triterpenoids is very important for testing their eventual (emphasis added) activity on human lymphocytes." No conclusive data on human activity had been established. Thus, the use of ethanol in extraction is insignificant to Dr. Mbah, et al.

5. Similarly, Dr. Ekpendu's group studied "hexane, ethyl acetate and methanol extracts of Napoleonaea imperialis, obtained from the root bark, not the extracts from the seeds themselves." As established in my patent application, the seeds were chosen by my group to obtain biologically active extracts showing antileishmanial activity.

6. A critical review of the referenced publications on *Napoleonaea imperialis* P.Beauv(Lecythidaceae) by Ekpendu *et al* (1998) and Kapundu *et al* (1980) revealed the following observations; first, the two groups of investigators were chemists and therefore were more interested on the chemistry of this plant rather than their biological or therapeutic

properties. Secondly, neither Ekpendu nor Kapundu screened for biological or pharmacological activities of the constituents of this plant. Also both groups used similar methods in their chemical investigation of the major constituents of *N. imperialis* known as saponins. In all, both referenced papers the saponins were first hydrolyzed before isolation and chemical identification of the constituents. It is remarkable to note that both groups worked on the hydrolyzed products (sapongenols/sapogenins/aglycones/genin) instead of the intact plant constituents (saponins). The implication of these approaches will be discussed in details. Some investigators adopted hydrolysis method because it eliminates the sugars resulting to simpler compounds. The product of hydrolysis is simpler, yielding lower molecular weight compounds, less polar, less complex structurally and easy to handle.

In contracts, as a pharmacognosist, I was particularly interested in the un-hydrolyzed, naturally occurring and pharmacological/ biological active plant constituents. My approach eliminated all processes of hydrolysis for compounds submitted for biological testing. In fact only naturally occurring pharmacologically active compounds were pursued further rather than hydrolyzed products. Bioassay directed-chromatographic fractionations of active extracts were

undertaken leading to the isolation of naturally occurring saponins hereby eliminating art fats.

To fully appreciate the distinction made above between the approaches adopted by Ekpendu and Kapundu while investigating *N. imperialis* seeds and root-bark respectively and that of mine investigating the seeds of *N. imperialis*, it is important to examine the constituents of this plant. Our present knowledge on *N. imperialis* indicated that the major constituents of this plant are the saponins, although there is very scanty information available in the literature on this plant.

Saponins are high-molecular-weight glycosides, consisting of a **sugar moiety** linked to a triterpene or steroid (**aglycone**).

Therefore, Saponin = Sugar + Aglycone (triterpene or steroid).

All saponins have in common the attachment of one or more sugars to the aglycone. Saponins are extremely widely distributed in the plant kingdom. Saponins occur in some plants which are used as human food. The list of biological activity associated with saponins is very long.

Saponin contents of different morphological plant part:

Plant secondary metabolites such as saponins, alkaloids, flavonoids etc have been report to vary in their distribution in different plant parts. In these examples, saponin contents have been reported to vary depending on factors such as the cultivar, the age, the physiological state and the geographical location of the plant (Hostettmann and Maraton, (1994)). Considerable variation in composition and quantity of saponins in vegetable material from different places, as documented for *Lonicera japonica* (Caprifoliaceace) has been reported (Kawai *et al.* 1998).

The saponin distribution among the organs of a plant may vary considerably. In the garden marigold (*Calendula officinalis*, Asteraceae), for example saponins with a glucuronic acid moiety at C-3 of oleanolic acid are founding the flowers, while a glucose moiety at the same position is found in the saponins from the roots (Lutomski, 1983; Vidal-Ollivier et al. 1989a,b). The flowers contain 3.57% saponins, while the roots have 2.55% of their dry weight in the form of saponins (Isaac, 1992). Ginsenoside levels in Panax ginseng (Araliaceae) are lowest in the leafstalks and stem (0.77%), intermediate in the main root (1.3%) and lateral roots (3.5%) and highest in the leaves (5.2%) and root hairs (6.1%) (Koizumi *et al.* 1982).

The above examples address some of the examiner's concerns with regards to the composition of different parts of the plant parts; root-barks vs seeds. Our work on Dracaena species revealed that very high saponin content are found mostly in the seeds (Okunji *et al* 1996)

Problems Associate with Hydrolysis: Method adopted by Ekpendu and Kapundu

Numerous chemical reactions and methods have been employed for breaking down saponins into smaller units for more ready analysis (Kitagawa 1981), one of such method is acid hydrolysis.

It is believed that once acid hydrolysis is completed, then the aglycone will be separated and identified. Many chemists including Ekpendu *et al* (1998) and Kapundu *et al* (1980) adopted hydrolysis of saponins prior to chemical characterization of plant constituents. However, there are some significant concerns such as artifacts formation, not being able to obtain genuine aglycone, possibility of epimerization, transformation etc. The following paragraphs will illustrate the above pitfalls in detail.

It has been reported that acid hydrolysis is not without risk because prolonged heating with an inorganic acid can give rise to complications involving artifact formation, low yields

and low selectivity (Tschesche and Wulff, 1972; Kitagawa, 1981). This is true not only of triterpene saponins but also of steroid saponins and saponins from marine organisms (Kitagawa *et al.* 1985b), often making the job of structure elucidation very complicated. A typical example from a study of the effects of various hydrolytic procedure on the sapogenin profile of soya saponins has shown that soyasapogenols B_1, C, D and E are probably formed as artifacts on aqueous hydrolysis of soya flour with hydrochloric acid in ethanol (Ireland *et al.* 1987). The true aglycones, soyasapogenols A and B are obtained by hydrolysis with sulphuric or hydrochloric acid in anhydrous methanol (Ireland and Dziedzic, 1986). Another problem arises during the acid hydrolysis of oleanolic acid and hederagenin glycosides in dioxin, giving rise to possible formation of lactone (Hiller *et al.* 1987). Similarly, Sulphuric acid on hydrolysis of hovenosides (glycosides of jujubogenin) gave a lactone, ebelin lactone (Inoue *et al.* 1978).

It is sometimes very difficult to obtain the genuine aglycones from the parent saponins. This problem is especially acute for the triterpenes containing a 13β, 28-oxide structure. Tscheshe and coworkers stated that it took a long time, for example, before the aglycone cyclamiretin A of cyclamen (from the tubers of *Cyclamen europaeum,* Primulaceae) was completely characterized (Tscheshe *et al.* 1966). Another example is the

case for other 13β, 28-oxide aglycones (protoprimulagenin A), saikogenin F, etc.), it could be easily ring-opened by acid to the corresponding 12-en-28-alcohol. Similarly Primulaginin A is most probably an artifact produced during hydrolysis of saponins containing protoprimulagenin A as aglycone (Tscheshe *et al.* 1983). It should be noted here, however, that not all 12-en-28-alcohol aglycones are artifacts.

On hydrolysis, an acid-catalysed double-bond migration in triterpenes can also occur. For example, some olean-12-enes are isomerized to olean-13(18)-enes with hydrochloric acid in aqueous ethanol (Kubota *et al.* 1969). Quallaic and echinocystic acids are both isomerized to the corresponding olean-13(18)-enes under these conditions (Kubota *et al* 1969).

Epimerization is possible during acid hydrolysis, as shown by the conversion of arjungenin (from the corresponding 28-glycoside) to tomentosic acid. This transformation proceeds through the pathway described by Mahato *et al.* 1990 and confirmed by the isolation of the intermediate lactone.

The transformation of cochalic acid to echinocystic acid is another example. It involves an epimerization at the 16-OH group and probably also occurs via a 28 → 16 lactone (Mahota *et al.* 1990).

These are very few examples of potential risk of isolating art facts instead of naturally occurring plant constituents

associated when adopting acid hydrolysis in duringphytochemical investigations. It is possible that some of the Ekpendu's compounds were artifacts. The compounds isolated by my method have been replicated several times.

In conclusion; as reported Ekpendu *et al* (1998), hydrolysis of both ethyl acetate and methanol extracts were undertaken leading to the isolation of series of less polar compounds when compared with unhydrolyzed compounds. Similarly, control hydrolysis was carried out by Kapundu *et al* (1980) leading to characterization of new "prosapogenins" napoleogenol and napoleogenin which were less polar relative to un- hydrolized counterpart.

The approach adopted by both Ekpendu *et al* (1998) and Kapundu *et al* (1980) differ significantly from mine in that in my investigation, no acid hydrolysis was used instead intact saponins were isolated and characterized. In addition biological testing was carried out leading to the identification of bioactive compounds. The distribution of secondary metabolites in different plant parts has been discussed above. The results showed that different constituents have been isolated from different plant parts.

7. These facts would have been corroborated by Dr. Ekpendu, who is known to me. However, due to extreme hardships, and all attempts to contact Dr. Ekpendu failed even during my several trips to Nigeria between 2000-2003. These hardships included economic and financial constraints, lack of communication or national database or national phonebook etc. Additionally several attempts to contact students (who had worked on the experiments leading to Dr. Ekpendu's results) also failed. Due to the lack of proper communication facilities and the absence of demographic databases, any information on these students were unattainable since they had subsequently graduated.

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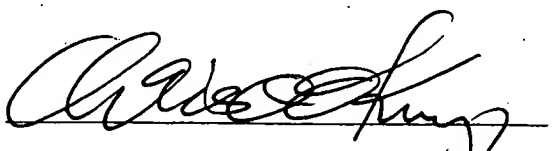
I further declare under penalty of perjury, pursuant to the laws of the United States of America, that the foregoing is true and correct, and that this declaration was executed by me on December 19, 2006, at Silver Spring Maryland.



Christopher O. Okunji

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS

EVIDENCE APPENDIX (E)(ii)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 03/28/2008

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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1655	

MAIL DATE	DELIVERY MODE
03/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/428,203	OKUNJI ET AL.	
	Examiner	Art Unit	
	Michele Flood	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 38* is/are pending in the application.

4a) Of the above claim(s) *2-10,13-29 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,12,30,31 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on November 30, 2007 with the cancellation of Claim 40.

The elected species, namely *Napoleonaea imperialis*, the solvent methanol and the seed portion of the plant, was not found; therefore, the elected invention was searched to the extent that the next species was found.

Claims 1, 11, 12, 30, 31 and 38 are under examination.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 11, 12, 30, 31 and 38, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Newly applied as necessitated by amendment.

Claim 1 is rendered indefinite by the phrase "A biologically active extract comprising a fractionation extract" because it is not clear as to the subject matter to which Applicant intends to seek patent protection. For example, plant material may be initially extracted with either water or methanol as a solvent in the making of a crude plant extract followed by subjecting the crude plant extract to fractionation with one or more solvents of increasing polarity or increasing strength. It would appear that

Applicant intends to direct the subject matter of the claimed invention to a biologically active extract comprising a fractionated extract from at least one plant selected from the claim-designated Markush group recited in Claim 1. The lack of clarity renders the claim ambiguous.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 12, 30 and 31, as amended, are rejected under 35 U.S.C. 102(b) as being anticipated by Okunji et al. (U). Newly applied as necessitated by amendment.

Applicant claims a biologically active extract comprising a fractionation extract from at least one plant selected from the group consisting of *Aframomum aulocacarpus, Aframomum danielli, Dracaena arborea, Eupatorium odoratum, Glossocalyx brevipes* and *Napoleonaea imperialis*, wherein the extract is obtained using an organic solvent, and wherein the biologically active extract is saponin-enriched and exhibits therapeutic anti-leishmanial activity. Applicant further claims a biologically active extract according to claim 1, wherein the extract is from at least one of roots, stem, bark, leaves, fruits or

seeds from the plant; wherein the solvent is selected from a group consisting of hexane, chloroform, ethyl acetate and methanol wherein the extract is obtained directly from solvent extraction of powdered seeds of the plant utilizing the solvent. Applicant further claims a biologically active extract according to claim 11, wherein the solvent is methanol.

Okunji teaches a saponin-enriched fraction of a methanol extract of powdered seed pulp obtained from *Dracaena arborea* (*see* abstract). On page 417, under "*Extraction and Isolation Protocol*", Okunji teaches that the powdered pulp plant material was directly extracted with methanol and that 'a portion of the methanol extract was first partitioned between chloroform-methanol-water mixture to yield a saponin-enriched lower organic layer which was concentrated to dryness *in vacuo* and lyophilized'. Okunji further teaches fractionation of the crude active saponin extract to obtain three spirostanol saponins, designated spiroconazole A, B and C. Okunji demonstrates that spiroconazole A exhibits anti-leishmanial activity (see Figures 4 and 5).

The reference anticipates the claimed subject matter.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele Flood
Primary Examiner
Art Unit 1655

MCF
March 24, 2008
/Michele Flood/
Primary Examiner, Art Unit 1655

Notice of References Cited

Application/Control No.	Applicant(s)/Patent Under Reexamination	
09/428,203	OKUNJI ET AL.	
Examiner	Art Unit	Page 1 of 1
Michele Flood	1655	

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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	N					
	O					
	P					
	Q					
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BIOLOGICAL ACTIVITY OF SAPONINS FROM TWO *DRACAENA* SPECIES

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ABSTRACT

Many species of the west African "soap tree" *Dracaena* are used in traditional medicine for the treatment of a variety of diseases. In continuation of our search for anti-infective agents from plants implicated in traditional medicine, we evaluated the biological activities of saponins from extracts of *Dracaena mannii* and *Dracaena arborea* by using a battery of test systems such as radiorespirometry, Cytosensor®, bioautography, and agar dilution methods and molluscicidal tests.

Bioassay-directed fractionation of the methanol extracts of seed pulp using a combination of chromatographic techniques, gel filtration, droplet countercurrent chromatography (DCCC), and low-pressure liquid chromatography (Lobar), led to the isolation and characterization of spiroconazole A, a pennogenin triglycoside [3β-*O*-{(α-L-rhamnopyranosyl(1→2),α-L-rhamnopyranosyl(1→3)-β-D-glucopyranosyl}-17α-hydroxyl-spirost-5-ene] (Fig. 1). As the active constituent, spiroconazole A exhibited pronounced antileishmanial, antimalarial, and molluscicidal activities. This paper also reports on the fungistatic, fungicidal and bacteriostatic activity of spiroconazole A against 17 species of fungi and 4 of bacteria.

INTRODUCTION

Available drugs for the treatment of diseases due to various protozoal infections are inadequate due to increasing parasite resistance and serious toxicity associated with some of them. In continuation of our screening program in search of anti-infective agents from plants implicated in traditional medicine, we evaluated the biological activities of saponins from extracts of *Dracaena mannii* and *D. arborea* using a battery of test systems (such as radiorespirometry, Cytosensor®, bioautography, and agar dilution methods, and

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Edited by Waller and Yamasaki, Plenum Press, New York, 1996

molluscicidal tests). The initial goal of this program was the identification of compounds having antifungal and molluscicidal properties. Previously, we reported one antifungal and several molluscicidal constituents of *D. mannii* (Okunji *et al.*, 1990, 1991).

Because antiprotozoal and antifungal activities are frequently associated with the same or chemically similar compounds, we considered it probable that spiroconazoles, the main saponin constituent of the two species of *Nigerian Dracaena*, would have antiprotozoal activity.

In general, antiprotozoals are not given high priority for commercial development because the per capita health expenditure in many tropical countries is less than the cost of one course of drug therapy. Thus, many "modern" antiparasitic drugs were initially marketed >40 years ago. Clinical intervention in the treatment of leishmaniasis, for example, is presently limited to the use of pentavalent antimonials (SbV), sodium stilbogluconate and *N*-methylglucamine antimonate, and secondarily, amphotericin B, or pentamidine (Croft, 1988; Bryceson, 1987). Treatment with these agents is not consistently effective, particularly for the most virulent leishmanial disease forms (Croft, 1988; Bryceson, 1987; Jha, 1983; Rocha *et al.*, 1980; Mebrahtu *et al.*, 1989). Furthermore, most of the current antiprotozoal drugs are very toxic. It would, therefore, be useful to develop more effective, less toxic, and orally active antileishmanials. The antileishmanial activity of the extracts from the Nigerian plant *Dracaena mannii* has been evaluated by determining their effect on parasite growth and on the catabolism of various substrates using the radiorespirometric microtest, RAM. The *in vitro* RAM, a metabolic test using leishmanial promastigotes (i.e. the monoflagellate extracellular culture forms shown in Fig. 2a), had been developed earlier in our laboratories. The RAM relies on drug inhibition of parasite production of $^{14}CO_2$ from a battery of ^{14}C-substrates to detect drug-mediated parasite damage at low drug concentration within a short time (Jackson *et al.*, 1989, 1990).

Another protozoan disease, malaria, remains the greatest human killer among parasitic infections, despite the world-wide effort to combat the disease and attempts at the eradication of the causative organisms. The emergence of multi-drug-resistant strains of *Plasmodium falciparum*, the most lethal of the malaria parasites, poses a serious health-care problem, not only in the malaria-endemic countries but also among international travellers.

Protozoan infections are also a major cause of mortality and morbidity in immunosuppressed patients, as in acquired immunodeficiency syndrome (AIDS). A single therapeutic agent active against different types of protozoa would be a major innovation in the treatment of these diseases.

Similarly, fungal and yeast infections are becoming increasingly resistant to modern drugs. In immunologically compromised individuals, for example, complications arising from uncontrollable fungal infections are among the leading cause of death. There is, therefore, a need for new and effective alternative treatment. This paper describes and summarizes our investigation of the therapeutic potential of these commonly used medicinal plants using a battery of biologic test systems.

MATERIALS AND METHODS

Plant Materials

Two species of *Dracaena, D. mannii* and *D. arborea*, were collected at Isi-elu, near the Nsukka campus of the University of Nigeria in February, 1985. The collection was chosen from plants listed in an ethnomedicinal survey carried out among the Igbo people (Iwu, 1981/82, 1993). The *Dracaena* spp. plants were taxonomically identified by Mr. A. Ozioko of the Department of Botany, University of Nigeria, Nsukka and the identities confirmed by Dr. J. C. Okafor of the Forestry Herbarium, Enugu. Voucher specimens have been deposited at t
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Antimalarial Bioassay

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have been deposited at the Department of Pharmacognosy Herbarium, University of Nigeria, Nsukka. Prior to extraction, the plant material was dried at 40 °C and the dried vegetable drug ground to coarse powder.

For column chromatography (CC), silica gel 60 size 0.063-0.200 mm (70-230 mesh ASTM, EM Science, was used, and Sephadex LH-20, Sigma, for gel filtration. Low-pressure liquid chromatography (Lobar) was done using a LichroPrep RP-8 column (40-63 mm 2.5 X 25 Merck) equipped with an FMI pump. DCCC equipment consisted of type 300 glass tubes (length 400 mm, I.D. 2 mm) (Tokyo Rikakikai, Nishikawa Bldg, Toyama-Cho, Kanda Chiyoda, Tokyo), solvent system: $CHCl_3$:MeOH:H_2O (7:13:8). The solvent systems for CC were all homogeneous. Thin-layer chromatography (TLC) was used on the Analtech normal phase 10 x 20 cm plates. The TLC plates were developed using solvent systems were: I. $CHCl_3$:MeOH:H_2O (65:40:5), and II. $CHCl_3$:MeOH:H_2O (40:10:1). Sephadex LH-20 gel (25-100 mm size; Sigma) filtration was performed using methanol as eluant.

Extraction and Isolation Protocol

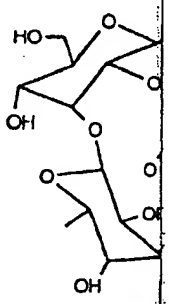
The powdered fruit pulp of the two species of *Dracaena* was Soxhlet-extracted with solvents of increasing order of polarity in two batches, starting with petroleum ether (bp 40-60 °C) (48 h), chloroform (48 h), ethyl acetate (48 h) and methanol (48 h). Each extract was concentrated to dryness *in vacuo* using a rotary evaporator at 40 °C. The isolation and purification of spiroconazole A, B, and C from *D. mannii* have been described elsewhere (Okunji *et al.*, 1991). Briefly, a portion of the methanol extract (20 g) was first partitioned between chloroform-methanol-water mixture (2:2:1) to yield a saponin-enriched lower organic layer which was concentrated to dryness *in vacuo* and lyophilized. Five grams of the active milky-colored fraction were dissolved in a minimum volume of methanol and chromatographed on a Sephadex LH-20 column (2.0 X 50 cm) with methanol as eluant. The flow rate was adjusted to 2.5 ml min-1 and 10-ml fractions were collected. One gram of the crude active saponin fraction was dissolved in 10 ml of a (1:1) mixture of both upper and lower phases of the solvent system chloroform-methanol-water (7:13:8) and then subjected to droplet countercurrent chromatography (DCCC) in the ascending mode. The more polar upper layer was used as the mobile phase. The sample was injected into the apparatus via a 15-ml sample chamber. The flow rate was 10 ml h-1, and the eluates were collected in 5-ml fractions. The monitoring of the fractions was carried out with TLC aluminum sheet silica gel 60-F254 in solvent systems I and II. The saponins were detected with Godin reagent (Godin, 1954). Low-pressure liquid chromatography on a Lichroprep RP-8 (40-63 mm) column was used as the final purification of the saponins. Two molluscicidal spirostanol saponins that we designated as spiroconazole A and B, and a third non-molluscicidal saponin, spiroconazole C, were isolated and characterized on the basis of spectroscopic evidence. Similar phytochemical and biological patterns were observed for *D. arborea*.

Antimalarial Bioassay

The *in vitro* antimalarial assays were performed by using a modification of the semi-automated microdilution technique described earlier (Desjardins *et al.*, 1979, Milhous *et al.*, 1985). Two *Plasmodium falciparum* malaria parasite clones, designated Indochina (W-2) and Sierra Leone (D-6), were utilized in susceptibility testing. The W-2 clone is resistant to chloroquine, pyrimethamine, sulfadoxine, and quinine, and the D-6 clone is resistant to mefloquine. The test compound, spiroconazole A, was dissolved in DMSO and serially diluted using malarial growth medium. Drug-induced reduction in uptake of tritiated hypoxanthine was used as an index of inhibition of parasite growth. In this assay,

Table 1. Antifungal activity of spiroconazole A, compared to current antifungal drugs: miconazole and ketoconazole. Both minimum inhibitory concentration , MIC, and minimum fungicidal concentration (MFC) are given in μg ml^{-1}. Adapted with permission from C.O. Okunji, C.N. Okeke, H.C. Gugnani, and M.M. Iwu, Int. J. Crude Drug Res. 28:193-199, 1990.

	Spiroconazole A		Miconazole		Ketoconazole	
Test Fungi	MIC (μg/ml)	MFC (μg/ml)	MIC (μg/ml)	MFC (μg/ml)	MIC (μg/ml)	MFC (μg/ml)
Dermatophytes						
Trichophyton mentagrophytes	12.50	25.00	6.25	25.00	6.25	25.00
Trichophyton tonsurans	12.50	50.00	1.56	6.25	0.78	3.13
Trichophyton soudanense	6.25	12.50	0.20	0.78	0.05	0.39
Trichophyton rubrum	12.50	25.00	3.13	6.25	1.56	6.25
Microsporum audouinii	12.50	25.00	1.56	3.13	0.20	0.39
Microsporum grpseum	50.00	100.00	12.50	100.00	0.30	1.56
Pathogenic Dermatiaceous Fungi						
Phialophora verrucosa (ATCC 50768)	50.00	100.00	0.05	0.20	0.10	0.20
Fonsecaes pedrosoi (ATCC 52593)	25.00	50.00	0.20	0.39	0.05	0.10
Cladosporium carrionii	12.50	12.50	0.10	0.39	0.10	0.30
Cladosporium tennuisimum (ATCC 623337)	100.00	100.00	0.78	3.13	0.39	0.78
Exophiala jeanselmei (ATCC 62791)	25.00	100.00	0.20	0.39	0.10	0.39
Ramichloridium subulatum (ATCC 62339)	25.00	1001.00	0.39	25.00	0.20	0.39
Yeasts						
Candida albicans	25.00	100.00	6.25	6.25	12.50	25.00
Candida tropicalis	100.00	100.00	6.25	6.25	1.56	1.56
Trichosporon cutaneum	6.25	6.25	0.05	0.02	0.02	0.78
Geotrichum candidum	12.50	12.50	1.56	1.56	0.39	0.78
Rhodotorula sp.	25.00	100.00	1.56	1.56	0.78	1.56



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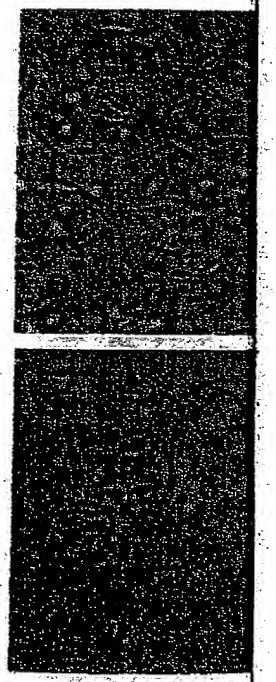

Fig. 2. Photograph sho
DMSO), and spiroconz
after 17.5 h drug exposu

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	Ketoconazole	
ıl)	MIC (μg/ml)	MFC (μg/ml)
10	6.25	25.00
5	0.78	3.13
8	0.05	0.39
5	1.56	6.25
3	0.20	0.39
00	0.30	1.56
)	0.10	0.20
)	0.05	0.10
)	0.10	0.30
3	0.39	0.78
)	0.10	0.39
10	0.20	0.39
5	12.50	25.00
5	1.56	1.56
2	0.02	0.78
5	0.39	0.78
5	0.78	1.56

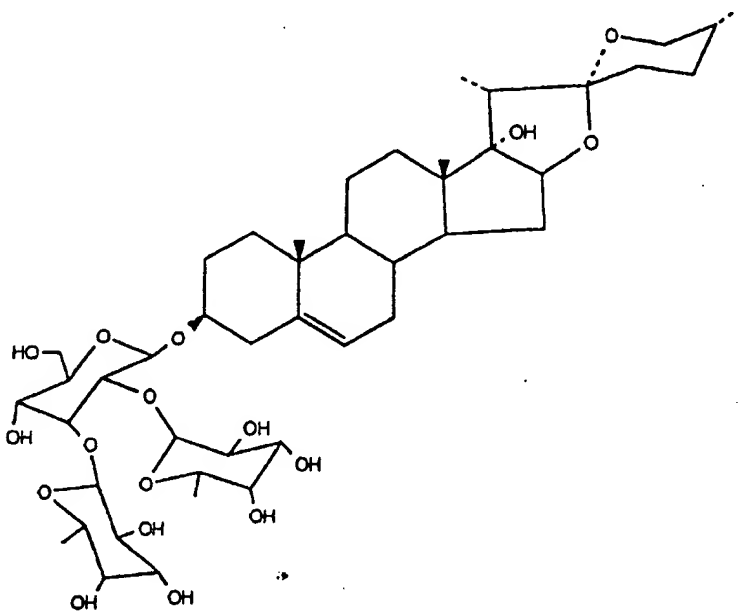

Fig. 1. Chemical structure of spiroconazole A.

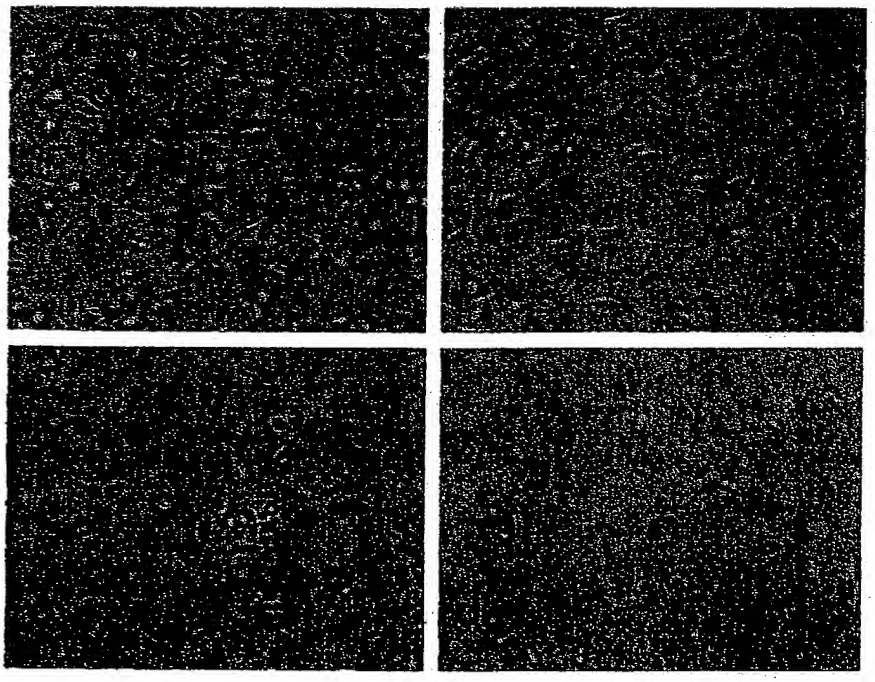

Fig. 2. Photograph showing leishmanial promastigote morphology of control (6a: 0.6% DMSO), and spiroconazole A-treated parasites (6b: 6.3-; 6c: 12.5-, and 6d: 50 μg ml^{-1}) after 17.5 h drug exposure during logarithmic phase growth.

the spiroconazole A treatment resulted in an IC_{50} value of 0.03 μg ml^{-1} for the W-2 clone, and 0.1μg ml^{-1} for the D-6 *Plasmodium falciparum* clone.

Antifungal Tests

TLC Bioassay:

A method similar to that of Homans and Fuchs (1970) was employed in this investigation. This technique involves direct spraying of thin layer chromatograms with conidial suspensions of a test organism. About 100 μg of extract was spotted on silica gel TLC plates and developed with solvent system I. Developed plates were separately sprayed with either a spore suspension of *Cladosporium cucumerinum*, and subsequently with spore suspensions of *Cladosporium carrionii, Cladosporium cladosporioides, Cladosporium tennuisimum* and *Fonsecaea pedrosoi*, to determine the spectrum of activity. The plates were then incubated in sealed humid chambers at room temperature for four days in the dark. Antifungal activity was manifested by the appearance of a white spot, corresponding to the position of the active compound, surrounded by a grey-black fungal growth all over the plates (Fig. 3). Bioassay-directed fractionation of the active extracts using a combination of chromatographic techniques led to the isolation and characterization of the spiroconazole group of compounds. The most active compound, spiroconazole A, gave a clearly visible inhibition zone at a concentration of 5 μg, which is below the limit of the detecting reagent (Godin's spray reagent).

Agar Diffusion Method:

The dermatiaceous fungi used in this work were environmental isolates (Okeke and Gugnani, 1986) and have been deposited in the American Type Culture Collection (ATCC). Culture accession numbers (designated ATCC#) are indicated in Table 1. The yeasts and dermatophytes were clinical isolates from the University of Nigeria Teaching Hospital, Enugu.

The antifungal activity of spiroconazole A was evaluated by the agar diffusion method using Emmon's Sabouraud dextrose agar (ESDA) as the growth medium. Stock solutions of the test compound and reference standard antifungal drugs, ketoconazole (R41,4001; lot C4,701) and miconazole (ZR-14,889; lot H1001), were prepared at initial concentrations of 10 X 10^3 μg ml^{-1} of dimethyl sulfoxide (DMSO). Serial 2-fold concentrations (0.025-100 μg ml^{-1}) were incorporated into the growth medium and plates were poured. ESDA incorporating only DMSO was used as control. Plates were inoculated with 0.05 ml of the fungal suspensions (approximately 10^5 conidia or hyphal elements/ml 0.9% sterile saline) in triplicate and incubated at 30 °C until macroscopically visible growth appeared in the control (48-96 h post incubation). The minimum inhibitory concentration (MIC) was the lowest concentration of compound that inhibited fungal growth. The minimum fungicidal concentration (MFC) was determined by culturing portions of the fungal inocula of the MIC test plates showing no sign of fungal growth onto fresh plates of ESDA in triplicate. The plates were incubated at 30 °C for 48-96 h. The lowest concentration at which the fungal inoculum yielded no visible growth was taken as the MFC.

In this assay, the most active analog, spiroconazole A, was shown effective against the yeasts and fungi at the drug concentrations listed in Table 1.

In Vitro Antileishmanial Activity

An *in vitro* radiorespirometric microtest (RAM) technique was used to evaluate the spiroconazoles for possible antileishmanial activity. This method, as already noted, relies

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Leishmania species/str

A clinical isolate of
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L-ornithine (1-^{14}C); (25) D
(1,4-^{14}C); and (46) Na-but
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RAM Drug Test Proced

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The results (Fig. 5) s
Leishmania strains at the d
inhibited the leishmanial ca
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on drug inhibition of parasite production of $^{14}CO_2$ from a battery of ^{14}C-substrates by promastigotes to detect drug-mediated parasite damage at low drug concentration within a short time. The test is quantitative, rapid, consistent, and is conducted in serum-free medium in which prior adaptation is not necessary to cultivate the so-called "difficult to grow" species.

Leishmania species/strains:

A clinical isolate of visceral *Leishmania (Leishmania) chagasi*, MHOM/BR/84/BA-13, was used for this study. This isolate was selected because sensitivity to SbV was previously determined using RAM. MHOM/BR/84/BA-13 is sensitive to Pentostam®, sodium antimony gluconate, at 6 μ ml^{-1} Sb (20 μg ml^{-1} drug); and to Glucantime®, *N*-methylglucamine antimonate, at 80 μg ml^{-1} Sb (286 μg ml^{-1}drug).

The ^{14}C-labelled substrates are (numerical codes given in the x-axis of Fig. 4) ^{14}C-substrates: (3) L-aspartic acid (4-^{14}C); (7) glycine (U-^{14}C); (**10**) L-leucine (1-^{14}C); (**13**) L-ornithine (1-^{14}C); (**25**) D-galactose (1-^{14}C); (**28**) D-mannose (1-^{14}C); (**44**) succinic acid (1,4-^{14}C); and (**46**) Na-butyrate (1-^{14}C). All ^{14}C-substrates were selected with specific activities as close to 40 mCi mM^{-1} per carbon atom as obtainable from commercial sources. The quantitative promastigote growth inhibition assay was used as a guide to identify isolates exhibiting antileishmanial activity.

RAM Drug Test Procedure:

The procedure was conducted as previously described (Jackson *et al.*, 1989, 1990). Promastigotes were maintained in log phase growth for 3 successive transfers (48-72 h apart) prior to radiorespirometric (RAM) testing. Test samples (or PBSS, 0.1 M phosphate-buffered balanced salt solution, plus drug solvent, DMSO, for parallel control cultures) was added 24 h after the third promastigote transfer to fresh growth medium. Incubation in the presence of plant samples was continued for 96 additional hours while the parasites remained in mid-log phase growth. The test compound was tested at 50 μg ml^{-1}. Drug sensitivity or resistance was based on ^{14}C-substrate(s) (listed above) for which $^{14}CO_2$ release was decreased for drug-treated parasites compared to parallel tests of phosphate-buffered balanced salt solution and vehicle (PBSS+DMSO) controls. Each experiment consisted of parallel: (a) duplicate tests of drug-treated parasites; plus (b) duplicate tests of drug vehicle control-treated parasites; plus (c) one "nonbiological" sterility control. The nonbiological control consisted of each ^{14}C-substrate (one substrate per microtiter tray well), and PBSS (the same PBSS batch used to wash, to suspend the parasites, and to make drug solution). Since there were no parasites in the nonbiological control, any $^{14}CO_2$ detected was attributed either to biologic contamination (or, less likely, chemical contamination) of the ^{14}C-substrates resulting in breakdown of such substrates. If radioactivity above background (10 dpm) was detected in the nonbiological control, the suspect solution(s) was replaced and the experiment was repeated.

The results (Fig. 5) show that spiroconazole A strongly inhibited the growth of the *Leishmania* strains at the dose of 50 μg ml^{-1}. This test compound also significantly inhibited the leishmanial catabolism of various ^{14}C-substrates, resulting in a maximum suppression of more than 95% when compared with the values observed for the controls (Fig. 4).

Antifungal Activity of *Dracaena mannii*
Fruit Pulp Against
Cladosporium cucumerinum

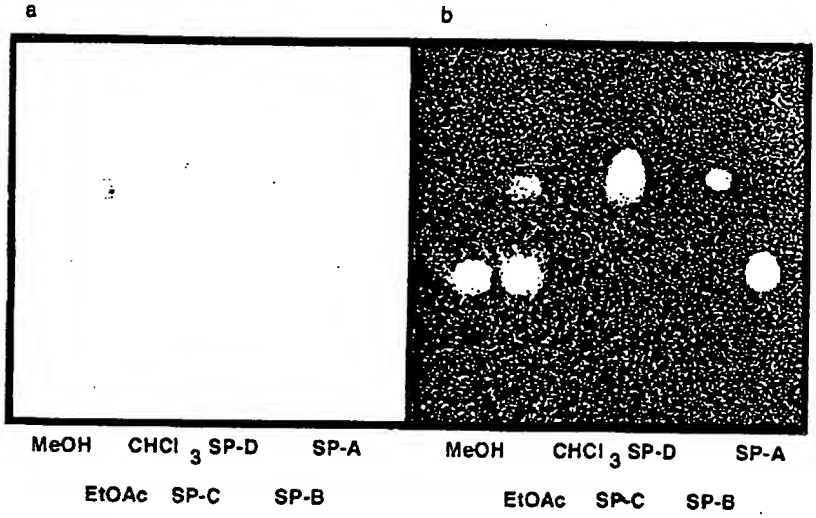


Fig 3. Thin layer chromatography (TLC)-bioassay on a silica gel plate, showing inhibition of the fungus, *Cladosporium cucumerinum*, by *Dracaena mannii* extracts and isolated compounds.

Leishmania (L.) chagasi, MHOM/BR/84/BA-13, MM2
MEDIUM, 96 h SPIROCONAZOLE A (50 µg/ml
0.32% DMSO FINAL CONCETRATION)

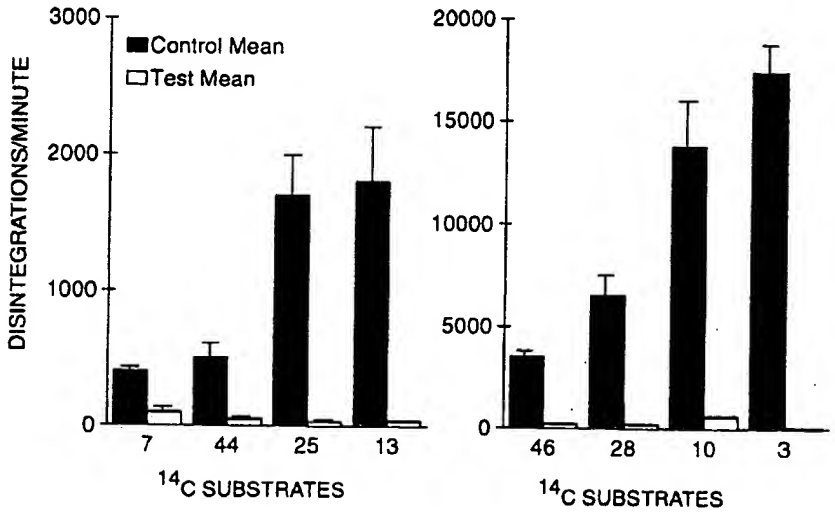
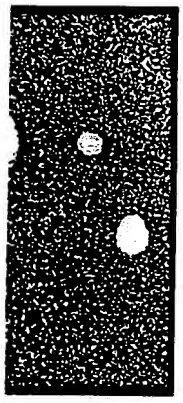


Fig. 4. Radiorespirometric (RAM) data showing markedly reduced respiration of *Leishmania (Leishmania)* chagasi, a visceral disease parasite after spiroconazole A treatment *in vitro*. The vehicle-control-treated parasite respiration is represented by the light grey vertical bars; the spiroconazole A (50 µg ml^{-1} for 96 h)-treated parasites, by the solid black bars. The ^{14}C-substrate numeric codes (x-axis) were given in the corresponding section of the Materials and Methods.



SP-D SP-A

C SP-B

:a gel plate, showing
ia mannii extracts and

), MM2
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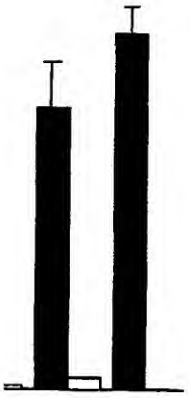

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Cytosensor Microphysiometer System

The rate at which cell excrete acids into their environment is closely linked to the rate which they convert food to energy, i.e their metabolic rate. The Cytosensor Microphysiometer System (CMS) measures the rate at which cells acidify their immediate environment. The CMS monitors these metabolic changes as changes in the rate of cellular acidification. In this way, the system provides a real-time, noninvasive means of measuring cellular responses to a wide variety of agents (McConnell *et al.*, 1992).

Spiroconazole A was tested for antileishmanial activity *in vitro* using CMS. Promastigote leishmanial forms were exposed to spiroconazole A in the chemically defined, serum-free medium (Jackson *et al.*, 1989) for 17.5 h during logarithmic growth phase. To prepare cells for CMS, the nonadherent cell protocol was utilized. Briefly, the cells were centrifugally concentrated, counted by hemacytometer, and resuspended in 0.2% low-temperature agarose in balanced salt solution. Leishmanial promastigotes, a 10-µl suspension containing 1-2 X 10^6 cells in agarose, were placed in each of 8 Cytosensor flow-chambers and the low-buffer formulation of RPMI medium (pH 7.4, Molecular Devices Corporation) was pumped over the cells. The repetitive pump cycle time was 2.0 min (88 sec of medium flow followed by 32 sec of pump off). During the 32 sec the peristaltic pump was not operating, the rate of leishmanial acidification of RPMI medium in each of 8 separate cell chambers was measured. Acidification rates during the two-min cycle resulted in less than 0.1 pH unit change and were not detrimental to the leishmanial cells. The CMS leishmanial acidification rates (representative data given in Fig. 6) were relatively constant for each drug treatment concentration (6.3, 12.5, 50 µg ml^{-1}) and vehicle control (0.6% DMSO) duplicate pair, tested in parallel simultaneously, over the 11-h observation period.

In Vivo Antileishmanial Activity

The *in vivo* antileishmanial activity was determined by administering various doses of the spiroconazole A to golden hamsters and determining the effect on laboratory-induced visceral and cutaneous leishmaniasis of the animals. For this assay, the compounds were tested against *Leishmania (Leishmania) donovani*, MHOM/SD/43/Khartoum, a causative organism of kala azar or visceral leishmaniasis, and *Leishmania (Viannia) panamensis*, MHOM/PA/83/WR539, an etiological agent of simple cutaneous leishmaniasis. Spiroconazole A was tested in each *in vivo* leishmanial model by the oral, intramuscular, and subcutaneous routes of administration.

The results of the activity of the spiroconazole A administered through the intramuscular route to hamsters infected with cutaneous *L. panamensis* represent an example of dose-dependent *in vivo* activity of the compound. At a dose of 104 mg kg^{-1} total dose (equivalent to 26 mg kg^{-1} per day) of the spiroconazole A, administered by intramuscular route twice a day for 4 days, the test substance produced a 73% inhibition of lesion caused by *L. panamensis* in hamsters. A dose of 52 mg kg^{-1} (13 mg kg^{-1} per day) by the same regimen gave a 51% reduction of the lesion area, and at a dose of 13 mg kg^{-1} (3.25 mg kg^{-1} per day) 7% reduction of the lesion area was observed.

Antibacterial Activity:

Antibacterial activity of spiroconazole A was evaluated by the agar well assay method using trypticase soy agar (Difco) as the growth medium. Plates of this medium were inoculated with 0.1 ml of a 6th culture of the test isolate in trypticase soy broth, a sterile glass spreader being used to ensure uniform growth of the inoculum. Wells (10 mm diameter) were made in the seeded agar plates and 0.1 ml of 1% solution of spiroconazole

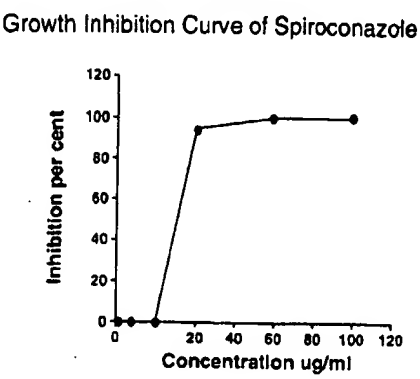

Fig. 5. Growth inhibition (y-axis) for *Leishmania (Leishmania)* chagasi with increasing spiroconazole A concentration (x-axis).

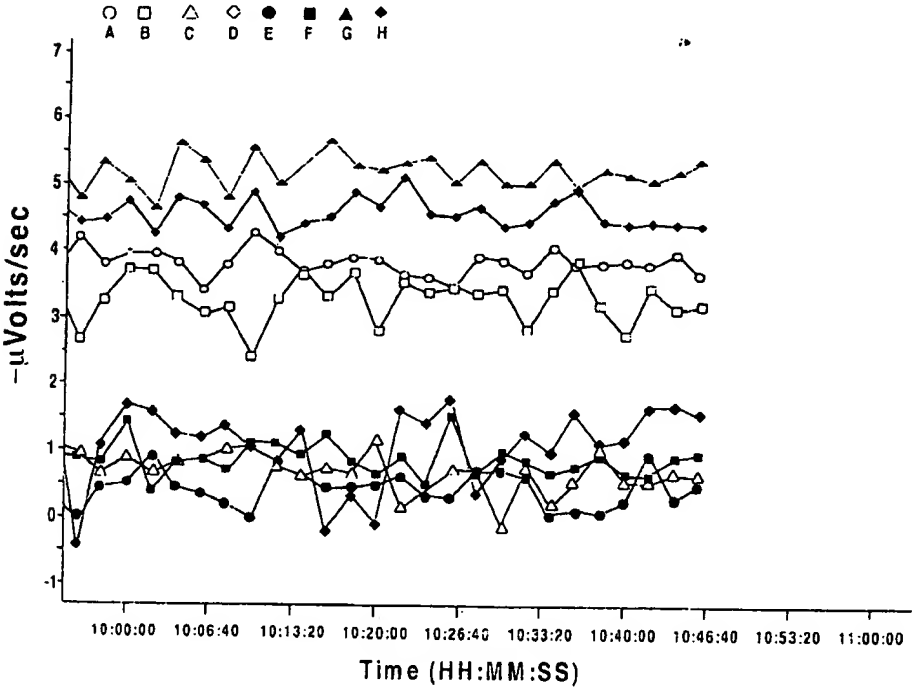

Fig. 6. Cytosensor microphysiometer (CMS) antileishmanial promastigote results after 17.5 h spiroconazole A treatment. The duplicate control parasite (i.e. parasites treated with drug solvent, 0.6% DMSO) tests, represented as uppermost lines, "G" and "H", have a consistently higher metabolic rate during the 11 h of observation. Parasites preincubated in parallel with controls for 17.5 h with 6.3- (lines "A" and "B"), 12.5- (lines "C" and "D"), and 50 µg ml^{-1} spiroconazole A (lines "E" and "F"), manifest lower metabolic rates, with the two highest drug concentrations resulting in metabolic rates very close to zero.

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RESULTS AND

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A in DMSO was introduced into the wells in triplicate. Streptomycin at a concentration of 100 μg ml^{-1} was used as reference standard and 0.1 ml DMSO as a control. The plates were incubated at 37 °C and the diameter of zones of inhibition was measured across each well after 24 h. The MIC for bacteria was determined in trypticase soy broth to which were added serial 2-fold concentrations (0.025-200 μg ml^{-1}) of spiroconazole A. The tubes were inoculated in triplicate with 0.01-ml quantities of 6th broth cultures of the test isolates. The tubes were incubated at 37 °C for 24 h and examined spectrophotometrically at 530 nm. The lowest drug concentration that showed no turbidity was taken as the MIC. Streptomycin was used as the standard reference drug.

Molluscicidal Potency Test

Two local snail vectors; *Bulinus globosus* and *Biomphalaria pfeifferi*, were collected from a pond near Nkalagu Cement Factory in the Isielu Local Government Area of Enugu State, Nigeria and reared in our laboratory. Living snails were identified to species by the staff of the Department of Zoology, University of Nigeria. The residue from methanol extracts of *Dracaena* fruit pulp and spiroconazole A were separately dissolved in distilled water. This was made into a stock solution of 100 ppm before serial dilution to obtain desired concentrations. Molluscicidal tests were carried out according to Duncan and Sturrock (1987) using laboratory-reared snails. Tests were carried out in two replicates per test compound concentration. Ten snails (6-10 mm in height) were exposed for 24 h allowing 24 h for the recovery period after which mortality rate was determined. Tests to evaluate the effects of physicochemical factors (UV and pH) on the molluscicidal activity of spiroconazole A were carried out as described by Adewunmi and Marquis (1980).

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RESULTS AND DISCUSSION

In a first activity-directed investigation, the methanol extracts of the fruit pulp of *D. mannii* and *D. arborea* exhibited strong antifungal and molluscicidal activities. Bioassay directed fractionation of this active fraction led to the isolation of a spiroconazole group of compounds. The antifungal activity of extracts of these plants was originally detected by direct spraying of TLC plates with a spore suspension of the test fungus *Cladosporium cucumerinum*. A clearly visible inhibition zone, even at the lowest concentration of 5 μg, was observed after using spiroconazole A (illustrated in Fig. 3). This concentration is below the detectable limit of the freqently used spray reagent (Godin, 1954) for saponins.

Spiroconazole A was tested for fungistatic, fungicidal and bacteriostatic activity against 17 species of fungi (results summarized in Table 1) and bacteria. These fungi, with the exception of *Cladosporium tennuisimum* and *Ramichloridium subulatum*, are well known either as strict or opportunistic pathogens of humans. The dermatophytes, causal agents of infections of hair, nail and skin, were inhibited at concentrations of 50 μg ml^{-1} or less, with Trichophyton soudanense manifesting greatest sensitivity to the drug (MIC; 6.25 μg ml^{-1}). The MICs for the species of pathogenic dermatiaceous fungi, causal agents of cutaneous and subcutaneous mycoses, were within the range 12.5-100 μg ml^{-1}. All the test yeasts species were inhibited at 100 μg ml^{-1} concentration or less, the most sensitive being Trichosporon cutaneum (MIC, 6.25 μg ml^{-1}). The minimum fungal concentrations were mostly 1-4 times the MIC values. The control antimycotics, ketoconazole and miconazole, commonly used in chemotherapy, showed lower MICs and MFCs relative to the test compound (Table 1). The result of the antibacterial test showed that spiroconazole A was selectively bacteriostatic against the gram-positive bacteria species at 10 X 10^3 μg ml-1 in

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the agar assay method. In this study no antibacterial activity was observed at 200 μg ml^{-1} saponin in the MIC assay.

Spiroconazole A possesses strong molluscicidal activity against all the snail vectors. At 5 ppm concentration it exhibited 100% mortality within three h against four species of snails *Bulinus globosus, Bulinus forskalii, Biomphalaria pfeifferii,* and *Lymnaea natalensis,* while *Biomphalaria glabrata* were less susceptible to the 5 ppm lethal dose. However, spiroconazole A at 6 ppm yielded a 100% kill within 24 h against *Biomphalaria glabrata.* It is worthy of note that *Lymnaea natalensis,* which transmits the economically important major animal disease, fascioliasis, is killed within 3 h at 5 ppm lethal dose by spiroconazole A.

The results of the RAM test for leishmanial parasites are given in Fig. 4. After a 96-h incubation with spiroconazole A, no live parasites were observed in culture and RAM respiratory rates for all ^{14}C-substrates reflect this lack of parasite viability. The metabolic rate for every ^{14}C-substrate by the spiroconazole-treated parasites is near zero (solid black bars). The drug-treated results are in sharp contrast to the vehicle control (0.6% DMSO) treated promastigote ^{14}C-substrate catabolism, which show high respiratory rates during the 30-min test period (solid grey bars).

The results using the Cytosensor (Fig. 6) agree well with visual observation of the parasites by light microscopy given in Fig. 2, and the growth inhibition curve, Fig. 5. The vehicle control parasites, Fig. 2a, manifest the typical spindle-shaped monoflagellate form of leishmanial promastigotes. Cell density of the control parasites in culture was 5 X 10^7 ml^{-1}. Motility of the parasites was virtually 100%. Figure 2b shows parasites treated for 17.5 h at 6.3 μg ml^{-1} spiroconazole A. It is evident that at 6.3 μg ml^{-1} drug there are fewer parasites, about half that of the control culture, or 2.5 X 10^7 ml^{-1}, representing marked growth inhibition by spiroconazole A. At 12.5 μg ml^{-1} drug, Fig. 2c, the few remaining parasites are swollen, granulated, and the cytoplasm appears transparent, possibly indicating loss of membrane integrity with cytoplasmic leakage. Little to no motility was seen in parasites treated with 12.5 μg ml^{-1} spiroconazole A, and parasite number in culture was only 5 X 10^5 ml^{-1}. At 50 μg ml^{-1} drug, Fig. 2d, no intact parasites are visible, only hollow parasite membranes, with no cytoplasm. Likewise, an IC_{50} of approximately 10 μg ml^{-1} was observed for the growth inhibition data, Fig. 5. Maximum achievable serum level for SbV drugs, current "drugs-of-choice" for antileishmanial therapy, has been determined to be 20 μg ml^{-1} 1-2 h post-administration (references reviewed in Jackson, *et al.*, 1989, 1990).

Comparative analyses of the polar extracts from *Dracaena* species demonstrated that the spiroconazole analogues are the major biologically active components. These biological effects can perhaps explain the traditional use of the these plant species in treating different skin diseases.

The yield of biologically active saponins in *Dracaena* species is very high, estimated at up to 30% of the fruit pulp. The highest potency levels are localized in the fruit pulp and the molluscicidal material can be produced on a pilot scale. *Dracaenas* are propagated by seed or vegetatively by stem cutting and are drought resistant. Furthermore, the plant is abundant in west Africa (Keay *et al.*, 1964, Hutchinson and Dalziel, 1958) and is well known to the local population as a medicinal plant. The ease of cultivation of this plant will be a positive advantage over better known saponin-producing plants such as endod. The demand for steroid-based drugs such as cortisone and other corticosteroids, sex hormones, cardiotonic glycosides, oral contraceptives has steadily increased. Steroids of plant origin constitute a major part of the raw material for the preparation of such drugs. There is no doubt that the high yield of steroidal saponin from *Dracaena* spp. may serve as starting material for the manufacture of steroids of therapeutic interest.

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ACKNOWLEDG

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In conclusion, we have shown broad spectrum activity for spiroconazole A, having antibacterial, antifungal, antimalarial, antileishmanial, and molluscicidal properties. The drug concentration at which this compound acts compares very favorably with drug activity levels for current modern antibacterial, antifungal, antiparasitic, and molluscicidal drugs.

ACKNOWLEDGEMENTS

This work was completed while C.O.O. held a National Research Council Associateship at the Walter Reed Army Institute of Research. C.O.O. gratefully acknowledges the financial support by University of Nigeria Senate, Internation Foundation for Science, and the International Cooperative Biodiversity Group Program (ICBG, sponsored by the United States National Institutes of Health, National Science Foundation, Agency for International Development, and the Fogarty International Center).

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INTRODUCTION

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UNITED STATES PATENT AND TRADEMARK OFFICE

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EVIDENCE APPENDIX (E)(ii)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 07/28/2008

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EXAMINER	
FLOOD, MICHELE C	

ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
07/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Interview Summary	Application No. 09/428,203	Applicant(s) OKUNJI ET AL.	
	Examiner Michele Flood	Art Unit 1655	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Michele Flood*. (3)_____.

(2) *Abby Bhattacharyya*. (4)_____.

Date of Interview: *24 July 2008*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *All pending claims*.

Identification of prior art discussed: *Okunji et al.*.

Agreement with respect to the claims f)☒ was reached. g)☐ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant's representative, Abby Bhattacharyya, proposes limiting the species recited in Claim 1 to Napoleonaea imperialis and cancelling Claims 2-10, 12-29 and 31-35. Amending the claims as discussed would appear to obviate the rejections of record and place Claims 1, 11, 30 and 38 in condition for allowance absent discovery of prior art that reads on the claimed subject matter.*\.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Michele Flood/
Primary Examiner, Art Unit 1655
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 08/21/2008

ELIZABETH A. ARWINE
USAMRMC
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EXAMINER	
FLOOD, MICHELE C	

ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
08/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief

Application No.	Applicant(s)	
09/428,203	OKUNJI ET AL.	
Examiner	**Art Unit**	
Michele Flood	1655	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 July 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,11,12,30,31 and 38*.
   Claim(s) withdrawn from consideration: *2-10,13-29 and 32-35*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicant's arguments are directed to limitations not entered.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Michele Flood/
Primary Examiner, Art Unit 1655

Continuation of 3. NOTE: Applicant's insertion of the limitation "fractionated" would require further search and/or consideration.

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7590 10/10/2008

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EXAMINER	
FLOOD, MICHELE C	

ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief

Application No.	Applicant(s)	
09/428,203	OKUNJI ET AL.	
Examiner	**Art Unit**	
Michele Flood	1655	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 August 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,11,12,30,31 and 38*.
   Claim(s) withdrawn from consideration: *2-10,13-29 and 32-35*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Applicant's arguments are directed to limitations not entered.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Michele Flood/
Primary Examiner, Art Unit 1655

Continuation of 3. NOTE: Applicant's insertion of the limitation "fractionated" would require further search and/or consideration122

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/428,203	10/27/1999	CHRISTOPHER O. OKUNJI	003/172/SAP	4366

7590 11/16/2009

ELIZABETH A. ARWINE
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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	**PAPER NUMBER**
1655	

MAIL DATE	DELIVERY MODE
11/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.	Applicant(s)	
09/428,203	OKUNJI ET AL.	
Examiner	**Art Unit**	
MICHELE FLOOD	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,30 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,30 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on July 24, 2009, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Terry A. McKelvey/

Supervisory Patent Examiner, Art Unit 1655

For the purpose of expeditious prosecution, the amendment filed on July 24, 2009 in the appeal brief after final has been entered. Acknowledgment is made of the cancellation of Claims 2-10, 12-29 and 31-35.

Claims 1, 11, 30 and 38 are under examination.

Claim Objections

Claim 30 is objected to because of the following informalities: There is an apparent omission of an ampersand in line 4 of Claim 30. Applicant may overcome the objection by adding and, before "wherein", in line 4 of Claim 30.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11, 30 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Kapundu et al. (Kapundu et al. Phytochemistry (1980); 19(4): 615-622. New triterpenoids from *Napoleonaea imperialis*.). Newly applied.

Applicant claims a biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent;

and wherein said biologically active is saponin-enriched and exhibits anti-leishmanial activity. Applicant further claims a biologically active extract according to claim 1, wherein said solvent is methanol, wherein said extract is obtained directed from solvent extraction of powdered seeds of said plant utilizing said solvent. Applicant further claims a biologically active extract according to claim 11, wherein said solvent is methanol.

Kapundu teaches a methanol extract from powdered seeds of *Napoleonaea imperialis*, on page 615, Column 2, lines 11-12. Kapundu also teaches that the methanolic powdered seed extract of the claim-designated plant comprises saponin. For instance, on page 615, last line bridging page 616, line 1, Kapundu teaches extracting the seeds of *Napoleonaea imperialis* with methanol and adding water to the methanolic extract to precipitate a saponin, which is separated by filtration. Applicant may argue that Kapundu does not teach that the prior art methanolic plant extract as a biologically active extract which exhibits therapeutic anti-leishmanial activity. However, the claim-designated functional effect is considered inherent to the extract taught by Kapundu because the source of the plant, the particular plant material from the source plant, and the solvent used in the making of the plant extract taught by Kapundu are one and the same as disclosed by Applicant. Therefore, a biologically active saponin-enriched extract comprising a fractionated methanol extract from powdered seeds of *Napoleonaea imperialis*, which exhibits therapeutic anti-leishmanial activity is deemed inherent to the Kapundu' extract. Thus, the Office would not be persuaded by Applicant's argument.

The reference anticipates the claimed subject matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE FLOOD whose telephone number is (571)272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

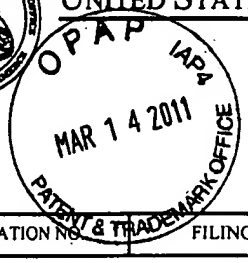
Michele Flood
Primary Examiner
Art Unit 1655

MCF
October 27, 2009

/Michele Flood/
Primary Examiner, Art Unit 1655

EVIDENCE APPENDIX (E) (ii)

UNITED STATES PATENT AND TRADEMARK OFF



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7590 06/04/2010

ELIZABETH A. ARWINE
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EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
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MAIL DATE	DELIVERY MODE
06/04/2010	PAPER

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Office Action Summary	Application No.	Applicant(s)	
	09/428,203	OKUNJI ET AL.	
	Examiner	Art Unit	
	MICHELE FLOOD	1655	

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Status

1)☒ Responsive to communication(s) filed on *16 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,30 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,30 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
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4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on March 16, 2010.

The objection set forth in the previous Office action mail dated November 16, 2009 has been overcome by Applicant's amendment to Claim 30.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 11, 30 and 38 are under examination.

Response to Arguments

Legal Standard for Anticipation/Inherency Under - 35 USC § 102

To anticipate a claim under 35 US.C. 102(b), a single prior art reference must place the invention in the public's possession by disclosing each and every element of the claimed invention in a manner sufficient to enable one skilled in the art to practice the invention. *Scripps Clinic & Research Foundation v. Genetech, Inc.,* 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1001 (Fed. Cir. 1991); *In re Donahue,* 766 F2d531, 533, 266 U.S.P.Q. 619, 621 (Fed. Cir. 1985). To anticipate, the prior art must either expressly or inherently disclose each limitation of the claimed invention, *MEHL/Biophile Int'l Corp. v. Milgraum,* 192F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1303 (Fed. Cir. 1999) (citing to *In re Schreiber,* 128 F.3d 1473, 1477, 44 U.S.P.Q. 1429, 1431 (Fed. Cir. 1997)); *Atlas Powder Co. v. Ireco, Inc.,* 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1946 (Fed. Cir. 1999). To inherently anticipate, the prior art, the prior art must necessarily

function in accordance with, or include, the claimed limitations. *MEHL/Biophile,* 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. However, it is not required that those of ordinary skill in the art recognize the inherent characteristics or the functions of the prior art. *Id.* Specifically, discovery of the mechanism underlying a known process does not make it patentable.

Claim Rejections - 35 USC § 102

Claims 1, 11, 30, as amended, and 38 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kapundu et al. (U; Translation of foreign language non-patent literature of Kapundu et al. Phytochemistry (1980); 19(4): 615-622. New triterpenoids from *Napoleonaea imperialis* provided herein.). The rejection remains for the reason set forth clearly in the previous Office action and repeated herein for convenience.

Applicant claims a biologically active extract comprising a fractionated extract from *Napoleonaea imperialis*, wherein said extract is obtained using an organic solvent; and wherein said biologically active is saponin-enriched and exhibits anti-leishmanial activity. Applicant further claims a biologically active extract according to claim 1, wherein said solvent is methanol, and wherein said extract is obtained directed from solvent extraction of powdered seeds of said plant utilizing said solvent. Applicant further claims a biologically active extract according to claim 11, wherein said solvent is methanol.

Applicant's main argument is directed to the idea that the Examiner has misapplied the inherency doctrine. Applicant further argues that the Examiner has not

responded to arguments set forth by Applicant in response to previous Office actions, with regard to the anticipatory teachings of Kapundu, et al. Applicant is mistaken. Applicant is invited to revisit the Non-Final Office action mail dated May 30, 2007 wherein the Examiner properly responded to each and every argument presented in Applicant's "REMARKS" filed on December 20, 2006, as well as its associated 1.132 declaration filed by Christopher O. Okunji, Ph. D.

Applicant further argues that the teachings of Kapundu '[are] is strictly dependent upon the hydrolyzed seed extracts of *N. imperialis'*. Applicant further argues limitations neither persuasive nor commensurate in scope to the limitations of the claimed invention, such as Applicant's pursuit of 'only naturally occurring pharmacologically active compounds . . . rather than hydrolyzed products . . . present knowledge on *N. imperialis* indicated that the major constituents of this plant are saponins . . . saponin contents have been reported to vary depending on factors (discussing geographic location) . . . saponin distribution among the organs of a plant may vary considerably (citing as example the variation in saponin concentration in marigold flowers varies significantly from that of the roots) . . . Our work on Dracaena species revealed that vary high saponin content are found mostly in the seeds." See Applicant's §132 affidavit at 6. Note also that Applicants specifically discuss the problems associated with hydrolysis of saponins as taught by Kapundu, et al. These include complications with artifact formation, low yields, low selectivity and difficulty with structure elucidation. See id at 8.' Applicant's arguments have been fully considered. However, Applicant's repeatedly raised in rebuttal arguments during prosecution are not relevant to the expressed

teachings of the reference. For instance, the Examiner has carefully considered Applicant's position that the Kapundu' reference fails to teach the instantly claimed invention and Applicant's reasoning for the distinction between what is disclosed by Applicant and what is taught by the prior art reference. However, Applicant's arguments are not persuasive because Kapundu clearly teaches a methanol extract from powdered seeds of *Napoleonaea imperialis*, on page 615, Column 2, lines 11-12. Furthermore, Kapundu expressly teaches that the methanolic powdered seed extract of the claim-designated plant comprises saponin. For example, on page 615, last line bridging page 616, line 1, Kapundu clearly teaches extracting the seeds of *Napoleonaea imperialis* with methanol and adding water to the methanolic extract to precipitate a saponin, which is separated by filtration. While Kapundu does teach identification of compounds contained therein the methanolic seed extract, thus necessitating a hydrolysis step of the extract, such disclosure by Kapundu does not negate the fact that Kapundu expressly teaches a methanolic extract obtained from powdered seeds of the claim-designated plant containing a saponin fraction therein. Therefore, while Kapundu does not expressly teach that the prior art methanolic plant extract has biological activity *per se*, biological activity is inherent to the extract taught by Kapundu because the source of the plant, the particular plant material from the source plant, and the solvent used in the making of the plant extract taught by Kapundu are one and the same as instantly claimed by Applicant. Therefore, antileishmanial activity extract of the methanolic extract of powdered seeds of *Napoleonaea imperialis* taught by Kapundu is inherent to the referenced extract, absent evidence to the contrary.

The reference anticipates the claimed subject matter.

No claims are allowed.

Applicant's summary of the most relevant portions of the prosecution history of the instant application and associated rebuttal arguments, with regard to Kapundu, is noted. Applicant asserts:

"In subsequent communications with the Examiner, namely a telephonic interview, Applicants' proposed amendments likely would have placed the application in condition for allowance. The Examiner noted that the only condition against allowance would be the discovery of prior art that reads on the claimed invention. *See* Interview Summary Record of July 24, 2008. However, the Examiner issued an Advisory Action on August 21, 2008, stating that the amendment was not entered because "Applicant's insertion of the limitation "fractionated" would require further search and/or consideration122". *See* Note 3 of the Advisory Action, August 21, 2008. Applicants filed an Appeal Brief on May 22, 2009, on several grounds, including the fact that the term "fractionated" was suggested by the Examiner in the Office Action of March 28, 2008, that initiated the telephonic interview, and the Applicants' reliance on the Examiner's explicit statements made in the Interview Summary Record. Kapundu, et al., is not mentioned in any of these communications.

Applicants respectfully traverse the Examiner's rejection and contend that the present Office Action is outside the scope of examination practices. While reopening of prosecution provides the Examiner a procedural mechanism to enter the claims, newly rejecting them on Kapundu, et al., is questionable as the amendments to the claims were addressed by the Examiner in the Telephonic Interview and the subsequent Advisory Action, neither of which mention the Kapundu, et al., reference. Furthermore, Applicants note that the Examiner presents the same inherency arguments (see rebuttal arguments below) that she had presented in her Office Actions prior to March 28, 2008, and ceased to continue thereafter. Such practices do not further prosecution and fail to provide Applicants the full and bona fide examination practices to which they are entitled.

Additionally, please note that the current Office Action makes no mention of the prior art rejection of the Office Action of March 28, 2008. Based on the prosecution history, it is the Applicants' strong position that the omission of the Kapundu, et al., reference in the March 28, 2008, Office Action, and the omission of the Okunji, et al., reference in the November 16, 2009, Office Action are explicit showings that both references have been overcome."

Applicant's arguments have been fully considered. However, with regard to the "Interview Summary" mail dated July 24, 2008, the record does not indicate the term "fractionated" was discussed, let alone any mention of the Examiner suggesting Applicant to amend the claims to recite "fractionated". While the Examiner did indeed

indicate 'Amending the claims as discussed would appear to obviate the rejections of record and place Claims 1, 11, 30 and 38 in condition for allowance absent discovery of prior art that reads on the claimed subject matter', the record shows that Applicant proposed limiting the species recited in Claim 1 to *Napoleonaea imperialis* and cancelling Claims 2-10, 12-29 and 31-35. Accordingly, the issuance of the Advisory Action mail dated August 21, 2008 was proper. Finally, in an Appeal Brief conference the Examiner along with Supervisory Patent Examiners Terry McKelvey and Jon Weber in attendance, upon review of the prior art made of record, it was determined that the Kapundu' reference read on the claimed invention. Thus, it was considered that expeditious prosecution of Applicant's claimed invention was best advanced by entering the amendment filed on July 24, 2009 in the Appeal brief.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELE FLOOD whose telephone number is (571)272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michele Flood
Primary Examiner
Art Unit 1655

MCF
June 2, 2010

/Michele Flood/
Primary Examiner, Art Unit 1655

Notice of References Cited	Application/Control No. 09/428,203	Applicant(s)/Patent Under Reexamination OKUNJI ET AL.	
	Examiner MICHELE FLOOD	Art Unit 1655	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
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	D	US-			
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	PTO 10-0557: Translation of "New Triterpenoids from Napoleona imperialis [Triterpenoides nouveaux de Napoleonaea imperialis]". Meuza Kapundu et al. Phytochemistry (1980); 19(4): 615-622. New triterpenoids from Napoleonaea imperialis. Translated By: The McElroy Translation Company (November 2009).
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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